

Performance of a multi-cancer early detection test in the randomized controlled NHS-Galleri trial

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Supplementary Information

Table of Contents

Tables.....	2
Supplementary Table S1. 12-Month Episode Sensitivity Metrics for the Subgroup of 12 Prespecified Cancer Types and Individual Cancer Types by Round and in Aggregate.	2
Supplementary Table S2. Performance Metrics by Subgroup: Age at Baseline.....	10
Supplementary Table S3. Performance Metrics by Subgroup: Sex.	13
Supplementary Table S4. Performance Metrics by Subgroup: Smoking Status.....	15
Supplementary Table S5. Performance Metrics by Subgroup: Prior Cancer History.	18
Supplementary Table S6. Performance Metrics by Subgroup: Race/Ethnicity.....	20
Supplementary Table S7. Performance Metrics by Subgroup: Index of Multiple Deprivation.	24
Supplementary Table S8. Performance Metrics by Subgroup: Education.....	28
Supplementary Table S9. PPV by CSO Prediction by Round and in Aggregate.....	33
Supplementary Table S10. Characteristics of First Primary Cancers in Participants.	39
Supplementary Table S11. Distribution of MCED-Detected Cancers by AJCC Cancer Types.	52
Supplementary Table S12. Distribution of Stage for Cancers per First-Cancer Diagnosed.....	55
Supplementary Table S13. Sensitivity Analysis for PPV by Screening Round and in Aggregate Accounting for Additionally Identified Recurrent Cancers.....	57
Supplementary Table S14. Exploratory Analysis for Participants With False-positive Results with Additional Follow-up.	58
Supplementary Table S15. Definitions of Screening Performance Metrics.	59
Figures	61
Supplementary Figure S1. Aggregate Episode Sensitivity by Cancer Type Diagnosed.	61
Supplementary Figure S2. Confusion Matrix of Predicted CSO vs Clinical CSO by Sex by Round and in Aggregate.	63
Supplementary Figure S3. Aggregate PPV by Predicted CSO.	68
Supplementary Figure S4. Stage and Type of Cancer Diagnosed Among Participants With True-Positive and False-Negative MCED Test Results.	70

Tables

Supplementary Table S1. 12-Month Episode Sensitivity Metrics for the Subgroup of 12 Prespecified Cancer Types and Individual Cancer Types by Round and in Aggregate.

	Participants with a cancer diagnosis		Episode sensitivity, ^a % (n/N) (95% CI)
	Positive MCED test result, n (%)	Negative MCED test result, n (%)	
Subgroup of 12 prespecified cancer types ^{b,c}			
First screening round	288 (68.7)	166 (23.4)	63.4 (288/454) (58.9, 67.7)
Second screening round	171 (65.5)	188 (26.8)	47.6 (171/359) (42.5, 52.8)
Third screening round	187 (72.8)	182 (25.9)	50.7 (187/369) (45.6, 55.7)
Aggregate	646 (68.9)	536 (25.4)	54.7 (646/1182) (51.8, 57.5)
Cancer type diagnosed			
First screening round (n=1127)			
Total, n	419	708	
Anus	3 (0.7)	2 (0.3)	60.0 (3/5) (23.1, 88.2)
Bladder	1 (0.2)	14 (2.0)	6.7 (1/15) (1.2, 29.8)
Breast	26 (6.2)	118 (16.7)	18.1 (26/144) (12.6, 25.1)
Cervix	1 (0.2)	1 (0.1)	1/2
Colon/Rectum	83 (19.8)	42 (5.9)	66.4 (83/125) (57.7, 74.1)
Gallbladder	5 (1.2)	4 (0.6)	55.6 (5/9) (26.7, 81.1)
Head and Neck	14 (3.3)	11 (1.6)	56.0 (14/25) (37.1, 73.3)
Kidney	8 (1.9)	22 (3.1)	26.7 (8/30) (14.2, 44.4)

	Participants with a cancer diagnosis		Episode sensitivity, ^a % (n/N) (95% CI)
	Positive MCED test result, n (%)	Negative MCED test result, n (%)	
Liver/Bile-duct	12 (2.9)	3 (0.4)	80.0 (12/15) (54.8, 93.0)
Lung	49 (11.7)	28 (4.0)	63.6 (49/77) (52.5, 73.5)
Lymphoid Leukaemia	13 (3.1)	14 (2.0)	48.1 (13/27) (30.7, 66.0)
Lymphoma	33 (7.9)	20 (2.8)	62.3 (33/53) (48.8, 74.1)
Melanoma	2 (0.5)	49 (6.9)	3.9 (2/51) (1.1, 13.2)
Myeloid Neoplasm	1 (0.2)	17 (2.4)	5.6 (1/18) (1.0, 25.8)
Oesophagus	20 (4.8)	7 (1.0)	74.1 (20/27) (55.3, 86.8)
Ovary	18 (4.3)	8 (1.1)	69.2 (18/26) (50.0, 83.5)
Pancreas	18 (4.3)	15 (2.1)	54.5 (18/33) (38.0, 70.2)
Plasma Cell Neoplasm	21 (5.0)	10 (1.4)	67.7 (21/31) (50.1, 81.4)
Prostate	48 (11.5)	236 (33.3)	16.9 (48/284) (13.0, 21.7)
Sarcoma	2 (0.5)	7 (1.0)	22.2 (2/9) (6.3, 54.7)
Stomach	9 (2.1)	5 (0.7)	64.3 (9/14) (38.8, 83.7)
Thyroid	1 (0.2)	4 (0.6)	20.0 (1/5) (3.6, 62.4)
Urothelial Tract	0	2 (0.3)	0/2
Uterus	7 (1.7)	25 (3.5)	21.9 (7/32) (11.0, 38.8)
Other ^d	3 (0.7)	30 (4.2)	9.1 (3/33) (3.1, 23.6)

	Participants with a cancer diagnosis		Episode sensitivity, ^a % (n/N) (95% CI)
	Positive MCED test result, n (%)	Negative MCED test result, n (%)	
Multiple Cancers	19 (4.5)	12 (1.7)	61.3 (19/31) (43.8, 76.3)
NCRAS Cancer of Unknown Primary ^e	2 (0.5)	2 (0.3)	2/4
Second screening round (n=969)			
Total, n	261	702	
Anus	3 (1.1)	1 (0.1)	3/4
Bladder	3 (1.1)	14 (2.0)	17.6 (3/17) (6.2, 41.0)
Breast	15 (5.7)	92 (13.1)	14.0 (15/107) (8.7, 21.8)
Cervix	1 (0.4)	1 (0.1)	1/2
Colon/Rectum	54 (20.7)	49 (7.0)	52.4 (54/103) (42.9, 61.8)
Gallbladder	2 (0.8)	1 (0.1)	2/3
Head and Neck	7 (2.7)	15 (2.1)	31.8 (7/22) (16.4, 52.7)
Kidney	1 (0.4)	19 (2.7)	5.0 (1/20) (0.9, 23.6)
Liver/Bile-duct	7 (2.7)	1 (0.1)	87.5 (7/8) (52.9, 97.8)
Lung	36 (13.8)	53 (7.5)	40.4 (36/89) (30.9, 50.8)
Lymphoid Leukaemia	7 (2.7)	13 (1.9)	35.0 (7/20) (18.1, 56.7)
Lymphoma	19 (7.3)	20 (2.8)	48.7 (19/39) (33.9, 63.8)
Melanoma	1 (0.4)	47 (6.7)	2.1 (1/48) (0.4, 10.9)
Myeloid Neoplasm	0	16 (2.3)	0.0 (0/16) (0.0, 19.4)

	Participants with a cancer diagnosis		Episode sensitivity, ^a % (n/N) (95% CI)
	Positive MCED test result, n (%)	Negative MCED test result, n (%)	
Oesophagus	10 (3.8)	4 (0.6)	71.4 (10/14) (45.4, 88.3)
Ovary	6 (2.3)	7 (1.0)	46.2 (6/13) (23.2, 70.9)
Pancreas	10 (3.8)	10 (1.4)	50.0 (10/20) (29.9, 70.1)
Plasma Cell Neoplasm	9 (3.4)	8 (1.1)	52.9 (9/17) (31.0, 73.8)
Prostate	33 (12.6)	242 (34.5)	12.0 (33/275) (8.7, 16.4)
Sarcoma	1 (0.4)	4 (0.6)	20.0 (1/5) (3.6, 62.4)
Stomach	6 (2.3)	4 (0.6)	60.0 (6/10) (31.3, 83.2)
Thyroid	0	7 (1.0)	0.0 (0/7) (0.0, 35.4)
Urothelial Tract	3 (1.1)	6 (0.9)	33.3 (3/9) (12.1, 64.6)
Uterus	6 (2.3)	20 (2.8)	23.1 (6/26) (11.0, 42.1)
Other ^f	8 (3.1)	30 (4.3)	21.1 (8/38) (11.1, 36.3)
Multiple Cancers	11 (4.2)	15 (2.1)	42.3 (11/26) (25.5, 61.1)
NCRAS Cancer of Unknown Primary ^e	2 (0.8)	3 (0.4)	40.0 (2/5) (11.8, 76.9)
Third screening round (n=961)			
Total, n	257	704	
Anus	1 (0.4)	0	1/1
Bladder	4 (1.6)	14 (2.0)	22.2 (4/18) (9.0, 45.2)
Breast	15 (5.8)	91 (12.9)	14.2 (15/106)

	Participants with a cancer diagnosis		Episode sensitivity, ^a % (n/N) (95% CI)
	Positive MCED test result, n (%)	Negative MCED test result, n (%)	
			(8.8, 22.0)
Cervix	0	1 (0.1)	0/1
Colon/Rectum	49 (19.1)	39 (5.5)	55.7 (49/88) (45.3, 65.6)
Gallbladder	7 (2.7)	3 (0.4)	70.0 (7/10) (39.7, 89.2)
Head and Neck	11 (4.3)	11 (1.6)	50.0 (11/22) (30.7, 69.3)
Kidney	4 (1.6)	15 (2.1)	21.1 (4/19) (8.5, 43.3)
Liver/Bile-duct	13 (5.1)	0	100 (13/13) (77.2, 100)
Lung	42 (16.3)	45 (6.4)	48.3 (42/87) (38.1, 58.6)
Lymphoid Leukaemia	5 (1.9)	5 (0.7)	50.0 (5/10) (23.7, 76.3)
Lymphoma	19 (7.4)	23 (3.3)	45.2 (19/42) (31.2, 60.1)
Melanoma	1 (0.4)	57 (8.1)	1.7 (1/58) (0.3, 9.1)
Myeloid Neoplasm	1 (0.4)	26 (3.7)	3.7 (1/27) (0.7, 18.3)
Oesophagus	12 (4.7)	10 (1.4)	54.5 (12/22) (34.7, 73.1)
Ovary	10 (3.9)	7 (1.0)	58.8 (10/17) (36.0, 78.4)
Pancreas	8 (3.1)	17 (2.4)	32.0 (8/25) (17.2, 51.6)
Plasma Cell Neoplasm	13 (5.1)	11 (1.6)	54.2 (13/24) (35.1, 72.1)
Prostate	22 (8.6)	235 (33.4)	8.6 (22/257) (5.7, 12.6)

	Participants with a cancer diagnosis		Episode sensitivity, ^a % (n/N) (95% CI)
	Positive MCED test result, n (%)	Negative MCED test result, n (%)	
Sarcoma	0	10 (1.4)	0.0 (0/10) (0.0, 27.8)
Stomach	4 (1.6)	1 (0.1)	80.0 (4/5) (37.6, 96.4)
Thyroid	0	8 (1.1)	0.0 (0/8) (0.0, 32.4)
Urothelial Tract	0	4 (0.6)	0/4
Uterus	4 (1.6)	17 (2.4)	19.0 (4/21) (7.7, 40.0)
Other ^g	3 (1.2)	32 (4.5)	8.6 (3/35) (3.0, 22.4)
Multiple Cancers	8 (3.1)	20 (2.8)	28.6 (8/28) (15.3, 47.1)
NCRAS Cancer of Unknown Primary ^e	1 (0.4)	2 (0.3)	1/3
Aggregate (n=3051)			
Total, n	937	2114	
Anus	7 (0.7)	3 (0.1)	70.0 (7/10) (39.7, 89.2)
Bladder	8 (0.9)	42 (2.0)	16.0 (8/50) (8.3, 28.5)
Breast	56 (6.0)	301 (14.2)	15.7 (56/357) (12.3, 19.8)
Cervix	2 (0.2)	3 (0.1)	40.0 (2/5) (11.8, 76.9)
Colon/Rectum	186 (19.9)	130 (6.1)	58.9 (186/316) (53.4, 64.1)
Gallbladder	14 (1.5)	8 (0.4)	63.6 (14/22) (43.0, 80.3)
Head and Neck	32 (3.4)	37 (1.8)	46.4 (32/69) (35.1, 58.0)
Kidney	13 (1.4)	56 (2.6)	18.8 (13/69)

	Participants with a cancer diagnosis		Episode sensitivity, ^a % (n/N) (95% CI)
	Positive MCED test result, n (%)	Negative MCED test result, n (%)	
			(11.4, 29.6)
Liver/Bile-duct	32 (3.4)	4 (0.2)	88.9 (32/36) (74.7, 95.6)
Lung	127 (13.6)	126 (6.0)	50.2 (127/253) (44.1, 56.3)
Lymphoid Leukaemia	25 (2.7)	32 (1.5)	43.9 (25/57) (31.8, 56.7)
Lymphoma	71 (7.6)	63 (3.0)	53.0 (71/134) (44.6, 61.2)
Melanoma	4 (0.4)	153 (7.2)	2.5 (4/157) (1.0, 6.4)
Myeloid Neoplasm	2 (0.2)	59 (2.8)	3.3 (2/61) (0.9, 11.2)
Oesophagus	42 (4.5)	21 (1.0)	66.7 (42/63) (54.4, 77.1)
Ovary	34 (3.6)	22 (1.0)	60.7 (34/56) (47.6, 72.4)
Pancreas	36 (3.8)	42 (2.0)	46.2 (36/78) (35.5, 57.1)
Plasma Cell Neoplasm	43 (4.6)	29 (1.4)	59.7 (43/72) (48.2, 70.3)
Prostate	103 (11.0)	713 (33.7)	12.6 (103/816) (10.5, 15.1)
Sarcoma	3 (0.3)	21 (1.0)	12.5 (3/24) (4.3, 31.0)
Stomach	19 (2.0)	10 (0.5)	65.5 (19/29) (47.3, 80.1)
Thyroid	1 (0.1)	19 (0.9)	5.0 (1/20) (0.9, 23.6)
Urothelial Tract	3 (0.3)	12 (0.6)	20.0 (3/15) (7.0, 45.2)
Uterus	17 (1.8)	62 (2.9)	21.5 (17/79) (13.9, 31.8)

	Participants with a cancer diagnosis		Episode sensitivity, ^a % (n/N) (95% CI)
	Positive MCED test result, n (%)	Negative MCED test result, n (%)	
Other ^h	14 (1.5)	92 (4.4)	13.2 (14/106) (8.0, 21.0)
Multiple Cancers	38 (4.1)	47 (2.2)	44.7 (38/85) (34.6, 55.3)
NCRAS Cancer of Unknown Primary ^e	5 (0.5)	7 (0.3)	41.7 (5/12) (19.3, 68.0)

Participants with multiple cancer diagnoses reported were categorized as “Multiple Cancers.”

^aEpisode sensitivity is not estimated for cancer types with less than 5 cases.

^bParticipants with multiple cancers are included in the subgroup of prespecified cancers only if all cancers belong to the subgroup.

^cAnus, bladder, colorectal, head and neck, liver/bile-duct, lung, lymphoma, oesophagus, ovary, pancreas, plasma cell neoplasm (myeloma), stomach.

^dOther cancer types include brain (n=13), mesothelioma (n=7), small intestine (n=4), vulva (n=4), ampulla of Vater (n=1), eyelid (n=1), penis (n=1), thymus (n=1), trachea (n=1).

^eNCRAS Cancer of Unknown Primary is defined as an invasive cancer with ICD-O-3 behaviour code 6 or 9; or an invasive cancer with behaviour code 3, topographical code C809 and unmapped cancer label.

^fOther cancer types include brain (n=11), mesothelioma (n=9), small intestine (n=6), germ cell (n=3), vulva (n=3), thymus (n=2), carotid body (n=1), penis (n=1), skin cancer (n=1), vagina (n=1).

^gOther cancer types include brain (n=8), mesothelioma (n=8), small intestine (n=6), skin cancer (n=3), vulva (n=3), adrenal (n=2), ampulla of Vater (n=2), penis (n=2), vagina (n=1).

^hOther cancer types include brain (n=32), mesothelioma (n=24), small intestine (n=16), vulva (n=10), penis (n=4), skin cancer (n=4), ampulla of Vater (n=3), germ cell (n=3), thymus (n=3), adrenal (n=2), vagina (n=2), carotid body (n=1), eyelid (n=1), trachea (n=1).

MCED, multi-cancer early detection; NCRAS, National Cancer Registration and Analysis Service.

Supplementary Table S2. Performance Metrics by Subgroup: Age at Baseline.

Screening round	Age 50–59y Estimate (n/N) (95% CI)	Age 60–69y Estimate (n/N) (95% CI)	Age 70–79y Estimate (n/N) (95% CI)
PPV			
First	57.9 (44/76) (46.7, 68.4)	58.3 (141/242) (52.0, 64.3)	57.9 (234/404) (53.1, 62.6)
Second	47.9 (23/48) (34.5, 61.7)	52.8 (95/180) (45.5, 59.9)	49.3 (143/290) (43.6, 55.0)
Third	40.0 (24/60) (28.6, 52.6)	51.3 (100/195) (44.3, 58.2)	43.5 (133/306) (38.0, 49.1)
Aggregate	49.5 (91/184) (42.3, 56.6)	54.5 (336/617) (50.5, 58.3)	51 (510/1,000) (47.9, 54.1)
NPV			
First	99.46 (18,416/18,516) (99.34, 99.56)	99.00 (27,723/28,004) (98.87, 99.11)	98.58 (22,756/23,083) (98.42, 98.73)
Second	99.46 (16,472/16,562) (99.33, 99.56)	98.91 (25,788/26,071) (98.78, 99.03)	98.46 (21,018/21,347) (98.28, 98.62)
Third	99.40 (16,016/16,113) (99.27, 99.51)	98.87 (25,009/25,295) (98.73, 98.99)	98.42 (20,033/20,354) (98.24, 98.59)
Aggregate	99.44 (50,904/51,191) (99.37, 99.50)	98.93 (78,520/79,370) (98.86, 99.00)	98.49 (63,807/64,784) (98.4, 98.58)
Episode sensitivity			
First	30.6 (44/144) (23.6, 38.5)	33.4 (141/422) (29.1, 38.0)	41.7 (234/561) (37.7, 45.8)
Second	20.4 (23/113) (14.0, 28.7)	25.1 (95/378) (21.0, 29.7)	30.3 (143/472) (26.3, 34.6)
Third	19.8 (24/121) (13.7, 27.8)	25.9 (100/386) (21.8, 30.5)	29.3 (133/454) (25.3, 33.6)
Aggregate	24.1 (91/378) (20.0, 28.6)	28.3 (336/1186) (25.8, 31.0)	34.3 (510/1487) (31.9, 36.7)
Specificity			
First	99.83 (18,416/18,448) (99.76, 99.88)	99.64 (27,723/27,824) (99.56, 99.70)	99.26 (22,756/22,926) (99.14, 99.36)

Screening round	Age 50–59y Estimate (n/N) (95% CI)	Age 60–69y Estimate (n/N) (95% CI)	Age 70–79y Estimate (n/N) (95% CI)
Second	99.85 (16,472/16,497) (99.78, 99.90)	99.67 (25,788/25,873) (99.59, 99.73)	99.31 (21,018/21,165) (99.18, 99.41)
Third	99.78 (16,016/16,052) (99.69, 99.84)	99.62 (25,009/25,104) (99.54, 99.69)	99.14 (20,033/20,206) (99.01, 99.26)
Aggregate	99.82 (50,904/50,997) (99.78, 99.85)	99.64 (78,520/78,801) (99.60, 99.68)	99.24 (63,807/64,297) (99.17, 99.30)
False-positive rate			
First	0.17 (32/18,448) (0.12, 0.24)	0.36 (101/27,824) (0.30, 0.44)	0.74 (170/22,926) (0.64, 0.86)
Second	0.15 (25/16,497) (0.10, 0.22)	0.33 (85/25,873) (0.27, 0.41)	0.69 (147/21,165) (0.59, 0.82)
Third	0.22 (36/16,052) (0.16, 0.31)	0.38 (95/25,104) (0.31, 0.46)	0.86 (173/2,0206) (0.74, 0.99)
Aggregate	0.18 (93/50,997) (0.15, 0.22)	0.36 (281/78,801) (0.32, 0.40)	0.76 (490/64,297) (0.70, 0.83)
MCED cancer detection rate			
First	0.24 (44/18,592) (0.18, 0.32)	0.5 (141/28,246) (0.42, 0.59)	1.00 (234/23,487) (0.88, 1.13)
Second	0.14 (23/16,610) (0.09, 0.21)	0.36 (95/26,251) (0.30, 0.44)	0.66 (143/21,637) (0.56, 0.78)
Third	0.15 (24/16,173) (0.10, 0.22)	0.39 (100/25,490) (0.32, 0.48)	0.64 (133/20,660) (0.54, 0.76)
Aggregate	0.18 (91/51,375) (0.14, 0.22)	0.42 (336/79,987) (0.38, 0.47)	0.78 (510/65,784) (0.71, 0.85)
MCED cancer signal detection rate			
First	0.41 (76/18,592) (0.33, 0.51)	0.86 (242/28,246) (0.76, 0.97)	1.72 (404/23,487) (1.56, 1.89)
Second	0.29 (48/16,610) (0.22, 0.38)	0.69 (180/26,251) (0.59, 0.79)	1.34 (290/21,637) (1.20, 1.50)
Third	0.37 (60/16,173) (0.29, 0.48)	0.77 (195/25,490) (0.67, 0.88)	1.48 (306/20,660) (1.33, 1.66)
Aggregate	0.36 (184/51,375)	0.77 (617/79,987)	1.52 (1000/65,784)

Screening round	Age 50–59y Estimate (n/N) (95% CI)	Age 60–69y Estimate (n/N) (95% CI)	Age 70–79y Estimate (n/N) (95% CI)
	(0.31, 0.41)	(0.71, 0.83)	(1.43, 1.62)

MCED, multi-cancer early detection; NPV, negative predictive value; PPV, positive predictive value.

Supplementary Table S3. Performance Metrics by Subgroup: Sex.

Screening round	Female Estimate (n/N) (95% CI)	Male Estimate (n/N) (95% CI)
PPV		
First	56.1 (162/289) (50.3, 61.7)	59.4 (257/433) (54.7, 63.9)
Second	51.7 (107/207) (44.9, 58.4)	49.5 (154/311) (44.0, 55.0)
Third	48.2 (105/218) (41.6, 54.8)	44.3 (152/343) (39.1, 49.6)
Aggregate	52.4 (374/714) (48.7, 56.0)	51.8 (563/1087) (48.8, 54.8)
NPV		
First	99.16 (34,749/35,043) (99.06, 99.25)	98.80 (34,146/34,560) (98.68, 98.91)
Second	99.18 (32,087/32,351) (99.08, 99.28)	98.62 (31,191/31,629) (98.48, 98.74)
Third	99.18 (31,076/31,333) (99.07, 99.27)	98.53 (29,982/30,429) (98.39, 98.66)
Aggregate	99.17 (97,912/98,727) (99.12, 99.23)	98.66 (95,319/96,618) (98.58, 98.73)
Episode sensitivity		
First	35.5 (162/456) (31.3, 40.0)	38.3 (257/671) (34.7, 42.0)
Second	28.8 (107/371) (24.5, 33.6)	26.0 (154/592) (22.6, 29.7)
Third	29.0 (105/362) (24.6, 33.9)	25.4 (152/599) (22.1, 29.0)
Aggregate	31.5 (374/1189) (28.9, 34.2)	30.2 (563/1862) (28.2, 32.4)
Specificity		
First	99.64 (34,749/34,876) (99.57, 99.69)	99.49 (34,146/34,322) (99.41, 99.56)
Second	99.69 (32,087/32,187) (99.62, 99.74)	99.50 (31,191/31,348) (99.41, 99.57)
Third	99.64 (31,076/31,189) (99.56, 99.70)	99.37 (29,982/30,173) (99.27, 99.45)
Aggregate	99.65 (97,912/98,252) (99.62, 99.69)	99.45 (95,319/95,843) (99.40, 99.50)

Screening round	Female Estimate (n/N) (95% CI)	Male Estimate (n/N) (95% CI)
False-positive rate		
First	0.36 (127/34,876) (0.31, 0.43)	0.51 (176/34,322) (0.44, 0.59)
Second	0.31 (100/32,187) (0.26, 0.38)	0.50 (157/31,348) (0.43, 0.59)
Third	0.36 (113/31,189) (0.30, 0.44)	0.63 (191/30,173) (0.55, 0.73)
Aggregate	0.35 (340/98,252) (0.31, 0.38)	0.55 (524/95,843) (0.50, 0.60)
MCED cancer detection rate		
First	0.46 (162/35,332) (0.39, 0.53)	0.73 (257/34,993) (0.65, 0.83)
Second	0.33 (107/32,558) (0.27, 0.40)	0.48 (154/31,940) (0.41, 0.56)
Third	0.33 (105/31,551) (0.28, 0.40)	0.49 (152/30,772) (0.42, 0.58)
Aggregate	0.38 (374/99,441) (0.34, 0.42)	0.58 (563/97,705) (0.53, 0.63)
MCED cancer signal detection rate		
First	0.82 (289/35,332) (0.73, 0.92)	1.24 (433/34,993) (1.13, 1.36)
Second	0.64 (207/32,558) (0.56, 0.73)	0.97 (311/31,940) (0.87, 1.09)
Third	0.69 (218/31,551) (0.61, 0.79)	1.11 (343/30,772) (1.00, 1.24)
Aggregate	0.72 (714/99,441) (0.67, 0.77)	1.11 (1087/97,705) (1.05, 1.18)

MCED, multi-cancer early detection; NPV, negative predictive value; PPV, positive predictive value.

Supplementary Table S4. Performance Metrics by Subgroup: Smoking Status.

Screening round	Currently smokes Estimate (n/N) (95% CI)	Formerly smoked Estimate (n/N) (95% CI)	Never smoked Estimate (n/N) (95% CI)
PPV			
First ^a	59.4 (38/64) (47.1, 70.5)	56.7 (174/307) (51.1, 62.1)	59 (207/351) (53.8, 64.0)
Second ^b	60.8 (31/51) (47.1, 73.0)	50.2 (118/235) (43.9, 56.6)	48.3 (112/232) (41.9, 54.7)
Third ^c	59.2 (29/49) (45.2, 71.8)	51.8 (133/257) (45.7, 57.8)	37.4 (95/254) (31.7, 43.5)
Aggregate ^d	59.8 (98/164) (52.1, 67.0)	53.2 (425/799) (49.7, 56.6)	49.5 (414/837) (46.1, 52.8)
NPV			
First ^a	98.96 (4568/4616) (98.62, 99.21)	98.90 (26,384/26,677) (98.77, 99.02)	99.04 (37,856/38,223) (98.94, 99.13)
Second ^b	98.82 (3846/3892) (98.43, 99.11)	98.72 (24,180/24,493) (98.57, 98.86)	99.05 (35,165/35,504) (98.94, 99.14)
Third ^c	98.76 (3596/3641) (98.35, 99.08)	98.67 (23,209/23,521) (98.52, 98.81)	99.00 (34,170/34,515) (98.89, 99.10)
Aggregate ^d	98.86 (12,010/12,149) (98.65, 99.03)	98.77 (73,773/74,691) (98.69, 98.85)	99.03 (107,191/108,242) (98.97, 99.09)
Episode sensitivity			
First ^a	44.2 (38/86) (34.2, 54.7)	37.3 (174/467) (33.0, 41.7)	36.1 (207/574) (32.2, 40.1)
Second ^b	40.3 (31/77) (30.0, 51.4)	27.4 (118/431) (23.4, 31.8)	24.8 (112/451) (21.1, 29.0)
Third ^c	39.2 (29/74) (28.9, 50.6)	29.9 (133/445) (25.8, 34.3)	21.6 (95/440) (18.0, 25.7)
Aggregate ^d	41.4 (98/237) (35.3, 47.7)	31.6 (425/1343) (29.2, 34.2)	28.3 (414/1465) (26.0, 30.6)
Specificity			

Screening round	Currently smokes Estimate (n/N) (95% CI)	Formerly smoked Estimate (n/N) (95% CI)	Never smoked Estimate (n/N) (95% CI)
First ^a	99.43 (4568/4594) (99.17, 99.61)	99.50 (26,384/26,517) (99.41, 99.58)	99.62 (37,856/38,000) (99.55, 99.68)
Second ^b	99.48 (3846/3866) (99.20, 99.66)	99.52 (24,180/24,297) (99.42, 99.60)	99.66 (35,165/35,285) (99.59, 99.72)
Third ^c	99.45 (3596/3616) (99.15, 99.64)	99.47 (23,209/23,333) (99.37, 99.55)	99.54 (34,170/34,329) (99.46, 99.60)
Aggregate ^d	99.45 (12,010/12,076) (99.31, 99.57)	99.50 (73,773/74,147) (99.44, 99.54)	99.61 (107,191/107,614) (99.57, 99.64)
False-positive rate			
First ^a	0.57 (26/4594) (0.39, 0.83)	0.50 (133/26,517) (0.42, 0.59)	0.38 (144/38,000) (0.32, 0.45)
Second ^b	0.52 (20/3866) (0.34, 0.80)	0.48 (117/24,297) (0.40, 0.58)	0.34 (120/35,285) (0.28, 0.41)
Third ^c	0.55 (20/3616) (0.36, 0.85)	0.53 (124/23,333) (0.45, 0.63)	0.46 (159/34,329) (0.40, 0.54)
Aggregate ^d	0.55 (66/12,076) (0.43, 0.69)	0.50 (374/74,147) (0.46, 0.56)	0.39 (423/107,614) (0.36, 0.43)
MCED cancer detection rate			
First ^a	0.81 (38/4,680) (0.59, 1.11)	0.64 (174/26,984) (0.56, 0.75)	0.54 (207/38,574) (0.47, 0.61)
Second ^b	0.79 (31/3,943) (0.55, 1.11)	0.48 (118/24,728) (0.40, 0.57)	0.31 (112/35,736) (0.26, 0.38)
Third ^c	0.79 (29/3,690) (0.55, 1.13)	0.56 (133/23,778) (0.47, 0.66)	0.27 (95/34,769) (0.22, 0.33)
Aggregate ^d	0.80 (98/12,313) (0.65, 0.97)	0.56 (425/75,490) (0.51, 0.62)	0.38 (414/109,079) (0.34, 0.42)
MCED cancer signal detection rate			
First ^a	1.37 (64/4,680) (1.07, 1.74)	1.14 (307/26,984) (1.02, 1.27)	0.91 (351/38,574) (0.82, 1.01)

Screening round	Currently smokes Estimate (n/N) (95% CI)	Formerly smoked Estimate (n/N) (95% CI)	Never smoked Estimate (n/N) (95% CI)
Second ^b	1.29 (51/3,943) (0.99, 1.70)	0.95 (235/24,728) (0.84, 1.08)	0.65 (232/35,736) (0.57, 0.74)
Third ^c	1.33 (49/3,690) (1.01, 1.75)	1.08 (257/23,778) (0.96, 1.22)	0.73 (254/34,769) (0.65, 0.83)
Aggregate ^d	1.33 (164/12,313) (1.14, 1.55)	1.06 (799/75,490) (0.99, 1.13)	0.77 (837/109,079) (0.72, 0.82)

^a87 participants with missing subgroup values are not included.

^b91 participants with missing subgroup values are not included.

^c86 participants with missing subgroup values are not included.

^dScreening episodes from participants with missing subgroup values are not included.

MCED, multi-cancer early detection; NPV, negative predictive value; PPV, positive predictive value.

Supplementary Table S5. Performance Metrics by Subgroup: Prior Cancer History.

Screening round	Prior cancer history	
	Yes Estimate (n/N) (95% CI)	No Estimate (n/N) (95% CI)
PPV		
First	36.5 (35/96) (27.5, 46.4)	61.3 (384/626) (57.5, 65.1)
Second	43.2 (32/74) (32.6, 54.6)	51.6 (229/444) (46.9, 56.2)
Third	22.6 (14/62) (14.0, 34.4)	48.7 (243/499) (44.3, 53.1)
Aggregate	34.9 (81/232) (29.1, 41.2)	54.6 (856/1569) (52.1, 57.0)
NPV		
First	98.89 (5076/5133) (98.56, 99.14)	98.99 (63,819/64,470) (98.91, 99.06)
Second	98.80 (4616/4672) (98.45, 99.08)	98.91 (58,662/59,308) (98.82, 98.99)
Third	98.45 (4392/4461) (98.05, 98.78)	98.89 (56,666/57,301) (98.80, 98.97)
Aggregate	98.72 (14,084/14,266) (98.53, 98.90)	98.93 (179,147/181,079) (98.88, 98.98)
Episode sensitivity		
First	38.0 (35/92) (28.8, 48.3)	37.1 (384/1035) (34.2, 40.1)
Second	36.4 (32/88) (27.1, 46.8)	26.2 (229/875) (23.4, 29.2)
Third	16.9 (14/83) (10.3, 26.3)	27.7 (243/878) (24.8, 30.7)
Aggregate	30.8 (81/263) (25.5, 36.6)	30.7 (856/2788) (29.0, 32.4)
Specificity		
First	98.81 (5076/5137) (98.48, 99.07)	99.62 (63,819/64,061) (99.57, 99.67)
Second	99.10 (4616/4658) (98.78, 99.33)	99.63 (58,662/58,877) (99.58, 99.68)
Third	98.92 (4392/4440) (98.57, 99.18)	99.55 (56,666/56,922) (99.49, 99.60)

Screening round	Prior cancer history	
	Yes Estimate (n/N) (95% CI)	No Estimate (n/N) (95% CI)
Aggregate	98.94 (14,084/14,235) (98.76, 99.09)	99.60 (179,147/179,860) (99.57, 99.63)
False-positive rate		
First	1.19 (61/5137) (0.93, 1.52)	0.38 (242/64,061) (0.33, 0.43)
Second	0.90 (42/4658) (0.67, 1.22)	0.37 (215/58,877) (0.32, 0.42)
Third	1.08 (48/4440) (0.82, 1.43)	0.45 (256/56,922) (0.40, 0.51)
Aggregate	1.06 (151/14,235) (0.91, 1.24)	0.40 (713/179,860) (0.37, 0.43)
MCED cancer detection rate		
First	0.67 (35/5229) (0.48, 0.93)	0.59 (384/65,096) (0.53, 0.65)
Second	0.67 (32/4746) (0.48, 0.95)	0.38 (229/59,752) (0.34, 0.44)
Third	0.31 (14/4523) (0.18, 0.52)	0.42 (243/57,800) (0.37, 0.48)
Aggregate	0.56 (81/14,498) (0.45, 0.69)	0.47 (856/18,2648) (0.44, 0.50)
MCED cancer signal detection rate		
First	1.84 (96/5229) (1.51, 2.24)	0.96 (626/65,096) (0.89, 1.04)
Second	1.56 (74/4746) (1.24, 1.95)	0.74 (444/59,752) (0.68, 0.82)
Third	1.37 (62/4523) (1.07, 1.75)	0.86 (499/57,800) (0.79, 0.94)
Aggregate	1.60 (232/14,498) (1.41, 1.82)	0.86 (1569/182,648) (0.82, 0.90)

MCED, multi-cancer early detection; NPV, negative predictive value; PPV, positive predictive value.

Supplementary Table S6. Performance Metrics by Subgroup: Race/Ethnicity.

Screening round	White Estimate (n/N) (95% CI)	Mixed or multiple ethnic groups Estimate (n/N) (95% CI)	Black, African, Caribbean or Black British Estimate (n/N) (95% CI)	Asian or Asian British Estimate (n/N) (95% CI)	Other ethnic group Estimate (n/N) (95% CI)
PPV^a					
First ^b	58.7 (407/693) (55.6, 62.3)	33.3 (2/6) (9.7, 70.0)	42.9 (3/7) (15.8, 75.0)	43.8 (7/16) (23.1, 66.8)	–
Second ^c	50.5 (253/501) (46.1, 54.9)	2/3	1/2	45.5 (5/11) (21.3, 72.0)	0/1
Third ^d	46.7 (249/533) (42.5, 51.0)	42.9 (3/7) (15.8, 75.0)	20.0 (1/5) (3.6, 62.4)	21.4 (3/14) (7.6, 47.6)	1/1
Aggregate ^e	52.6 (909/1727) (50.3, 55.0)	43.8 (7/16) (23.1, 66.8)	35.7 (5/14) (16.3, 61.2)	36.6 (15/41) (23.6, 51.9)	1/2
NPV					
First ^b	98.98 (64,470/65,134) (98.90, 99.05)	98.68 (749/759) (97.59, 99.28)	98.69 (983/996) (97.78, 99.24)	99.18 (2299/2318) (98.72, 99.47)	99.36 (309/311) (97.69, 99.82)
Second ^c	98.89 (59,588/60,259) (98.80, 98.97)	99.53 (634/637) (98.62, 99.84)	98.88 (793/802) (97.88, 99.41)	99.23 (1929/1944) (98.73, 99.53)	100 (249/249) (98.48, 100)
Third ^d	98.84 (57,436/58,110) (98.75, 98.92)	99.37 (629/633) (98.39, 99.75)	98.73 (779/789) (97.68, 99.31)	99.26 (1885/1899) (98.77, 99.56)	100 (248/248) (98.47, 100)

Screening round	White Estimate (n/N) (95% CI)	Mixed or multiple ethnic groups Estimate (n/N) (95% CI)	Black, African, Caribbean or Black British Estimate (n/N) (95% CI)	Asian or Asian British Estimate (n/N) (95% CI)	Other ethnic group Estimate (n/N) (95% CI)
Aggregate ^e	98.91 (181,494/183,503) (98.86, 98.95)	99.16 (2012/2029) (98.66, 99.48)	98.76 (2555/2587) (98.26, 99.12)	99.22 (6113/6161) (98.97, 99.41)	99.75 (806/808) (99.10, 99.93)
Episode sensitivity^a					
First ^b	38.0 (407/1071) (35.1, 40.9)	16.7 (2/12) (4.7, 44.8)	18.8 (3/16) (6.6, 43.0)	26.9 (7/26) (13.7, 46.1)	0/2
Second ^c	27.4 (253/924) (24.6, 30.3)	40.0 (2/5) (11.8, 76.9)	10.0 (1/10) (1.8, 40.4)	25.0 (5/20) (11.2, 46.9)	—
Third ^d	27.0 (249/923) (24.2, 29.9)	42.9 (3/7) (15.8, 75.0)	9.1 (1/11) (1.6, 37.7)	17.6 (3/17) (6.2, 41.0)	1/1
Aggregate ^e	31.2 (909/2918) (29.5, 32.9)	29.2 (7/24) (14.9, 49.2)	13.5 (5/37) (5.9, 28.0)	23.8 (15/63) (15.0, 35.6)	1/3
Specificity					
First ^b	99.56 (64,470/64,756) (99.50, 99.61)	99.47 (749/753) (98.64, 99.79)	99.59 (983/987) (98.96, 99.84)	99.61 (2299/2308) (99.26, 99.79)	100 (309/309) (98.77, 100)
Second ^c	99.59 (59,588/59,836) (99.53, 99.63)	99.84 (634/635) (99.11, 99.97)	99.87 (793/794) (99.29, 99.98)	99.69 (1929/1935) (99.33, 99.86)	99.60 (249/250) (97.77, 99.93)
Third ^d	99.51 (57,436/57,720) (99.45, 99.56)	99.37 (629/633) (98.39, 99.75)	99.49 (779/783) (98.69, 99.80)	99.42 (1885/1896) (98.96, 99.68)	100 (248/248) (98.47, 100)

Screening round	White Estimate (n/N) (95% CI)	Mixed or multiple ethnic groups Estimate (n/N) (95% CI)	Black, African, Caribbean or Black British Estimate (n/N) (95% CI)	Asian or Asian British Estimate (n/N) (95% CI)	Other ethnic group Estimate (n/N) (95% CI)
Aggregate ^e	99.55 (181,494/182,312) (99.52, 99.58)	99.55 (2012/2021) (99.16, 99.77)	99.65 (2555/2564) (99.33, 99.82)	99.58 (6113/6139) (99.38, 99.71)	99.88 (806/807) (99.3, 99.98)
False-positive rate					
First ^b	0.44 (286/64,756) (0.39, 0.50)	0.53 (4/753) (0.21, 1.36)	0.41 (4/987) (0.16, 1.04)	0.39 (9/2308) (0.21, 0.74)	0 (0/309) (0, 1.23)
Second ^c	0.41 (248/59,836) (0.37, 0.47)	0.16 (1/635) (0.03, 0.89)	0.13 (1/794) (0.02, 0.71)	0.31 (6/1935) (0.14, 0.67)	0.40 (1/250) (0.07, 2.23)
Third ^d	0.49 (284/57,720) (0.44, 0.55)	0.63 (4/633) (0.25, 1.61)	0.51 (4/783) (0.20, 1.31)	0.58 (11/1896) (0.32, 1.04)	0 (0/248) (0, 1.53)
Aggregate ^e	0.45 (818/182,312) (0.42, 0.48)	0.45 (9/2,021) (0.23, 0.84)	0.35 (9/2564) (0.18, 0.67)	0.42 (26/6,139) (0.29, 0.62)	0.12 (1/807) (0.02, 0.70)
MCED cancer detection rate					
First ^b	0.62 (407/65,827) (0.56, 0.68)	0.26 (2/765) (0.07, 0.95)	0.30 (3/1003) (0.10, 0.88)	0.30 (7/2,334) (0.15, 0.62)	0 (0/311) (0, 1.22)
Second ^c	0.42 (253/60,760) (0.37, 0.47)	0.31 (2/640) (0.09, 1.13)	0.12 (1/804) (0.02, 0.70)	0.26 (5/1955) (0.11, 0.60)	0 (0/250) (0, 1.51)
Third ^d	0.42 (249/58,643) (0.38, 0.48)	0.47 (3/640) (0.16, 1.37)	0.13 (1/794) (0.02, 0.71)	0.16 (3/1931) (0.05, 0.46)	0.40 (1/249) (0.07, 2.24)
Aggregate ^e	0.49 (909/185,230) (0.46, 0.52)	0.34 (7/2045) (0.17, 0.70)	0.19 (5/2601) (0.08, 0.45)	0.24 (15/6202) (0.15, 0.40)	0.12 (1/810) (0.02, 0.70)

Screening round	White Estimate (n/N) (95% CI)	Mixed or multiple ethnic groups Estimate (n/N) (95% CI)	Black, African, Caribbean or Black British Estimate (n/N) (95% CI)	Asian or Asian British Estimate (n/N) (95% CI)	Other ethnic group Estimate (n/N) (95% CI)
MCED cancer signal detection rate					
First ^b	1.05 (693/65,827) (0.98, 1.13)	0.78 (6/765) (0.36, 1.70)	0.70 (7/1003) (0.34, 1.43)	0.69 (16/2334) (0.42, 1.11)	0 (0/311) (0, 1.22)
Second ^c	0.82 (501/60,760) (0.76, 0.90)	0.47 (3/640) (0.16, 1.37)	0.25 (2/804) (0.07, 0.90)	0.56 (11/1955) (0.31, 1.00)	0.40 (1/250) (0.07, 2.23)
Third ^d	0.91 (533/58,643) (0.84, 0.99)	1.09 (7/640) (0.53, 2.24)	0.63 (5/794) (0.27, 1.47)	0.73 (14/1913) (0.44, 1.22)	0.40 (1/249) (0.07, 2.24)
Aggregate ^e	0.93 (1,727/185,230) (0.89, 0.98)	0.78 (16/2045) (0.48, 1.27)	0.54 (14/2601) (0.32, 0.90)	0.66 (41/6202) (0.49, 0.90)	0.25 (2/810) (0.07, 0.90)

Metrics are not reported if N = 0.

^aMetrics are not estimated for subgroups with less than 5 cases.

^b85 participants with missing subgroup values are not included.

^c89 participants with missing subgroup values are not included.

^d84 participants with missing subgroup values are not included.

^eScreening episodes from participants with missing subgroup values are not included.

MCED, multi-cancer early detection; NPV, negative predictive value; PPV, positive predictive value.

Supplementary Table S7. Performance Metrics by Subgroup: Index of Multiple Deprivation.

Screening round	Quintile 1 Estimate (n/N) (95% CI)	Quintile 2 Estimate (n/N) (95% CI)	Quintile 3 Estimate (n/N) (95% CI)	Quintile 4 Estimate (n/N) (95% CI)	Quintile 5 Estimate (n/N) (95% CI)
PPV					
First ^a	56.7 (93/164) (49.1, 64.1)	55.2 (79/143) (47.1, 63.2)	58.8 (80/136) (50.4, 66.7)	61.6 (90/146) (53.6, 69.1)	57.9 (77/133) (49.4, 65.9)
Second ^b	48.2 (54/112) (39.2, 57.4)	52.5 (52/99) (42.8, 62.1)	52.2 (59/113) (43.1, 61.2)	51.0 (53/104) (41.5, 60.4)	48.3 (43/89) (38.2, 58.5)
Third ^c	45.8 (60/131) (37.5, 54.3)	40.2 (47/117) (31.7, 49.2)	51.3 (58/113) (42.2, 60.3)	50.0 (50/100) (40.4, 59.6)	41.8 (41/98) (32.6, 51.7)
Aggregate ^d	50.9 (207/407) (46.0, 55.7)	49.6 (178/359) (44.4, 54.7)	54.4 (197/362) (49.3, 59.5)	55.1 (193/350) (49.9, 60.3)	50.3 (161/320) (44.9, 55.8)
NPV					
First ^a	99.04 (15,548/15,699) (98.87, 99.18)	98.89 (13,486/13,637) (98.70, 99.06)	99.11 (14,620/14,751) (98.95, 99.25)	98.99 (13,927/14,069) (98.81, 99.14)	98.84 (11,085/11,215) (98.63, 99.02)
Second ^b	98.97 (13,775/13,918) (98.79, 99.13)	98.92 (12,298/12,432) (98.72, 99.09)	99.00 (13,525/13,661) (98.82, 99.16)	98.80 (13,023/13,181) (98.60, 98.97)	98.77 (10,456/10,586) (98.54, 98.96)
Third ^c	98.95 (13,275/13,416) (98.76, 99.11)	98.89 (11,809/11,942) (98.68, 99.06)	98.75 (13,071/13,237) (98.54, 98.92)	98.87 (12,596/12,740) (98.67, 99.04)	98.83 (10,106/10,226) (98.60, 99.02)
Aggregate ^d	98.99 (42,598/43,033) (98.89, 99.08)	98.90 (37,593/38,011) (98.79, 99.00)	98.96 (41,216/41,649) (98.86, 99.05)	98.89 (39,546/39,990) (98.78, 98.99)	98.81 (31,647/32,027) (98.69, 98.93)

Screening round	Quintile 1 Estimate (n/N) (95% CI)	Quintile 2 Estimate (n/N) (95% CI)	Quintile 3 Estimate (n/N) (95% CI)	Quintile 4 Estimate (n/N) (95% CI)	Quintile 5 Estimate (n/N) (95% CI)
Episode sensitivity					
First ^a	38.1 (93/244) (32.2, 44.3)	34.3 (79/230) (28.5, 40.7)	37.9 (80/211) (31.6, 44.6)	38.8 (90/232) (32.8, 45.2)	37.2 (77/207) (30.9, 44.0)
Second ^b	27.4 (54/197) (21.7, 34.0)	28 (52/186) (22.0, 34.8)	30.3 (59/195) (24.2, 37.0)	25.1 (53/211) (19.7, 31.4)	24.9 (43/173) (19.0, 31.8)
Third ^c	29.9 (60/201) (24.0, 36.5)	26.1 (47/180) (20.2, 33.0)	25.9 (58/224) (20.6, 32.0)	25.8 (50/194) (20.1, 32.4)	25.5 (41/161) (19.4, 32.7)
Aggregate ^d	32.2 (207/642) (28.7, 36.0)	29.9 (178/596) (26.3, 33.7)	31.3 (197/630) (27.8, 35.0)	30.3 (193/637) (26.9, 34.0)	29.8 (161/541) (26.1, 33.7)
Specificity					
First ^a	99.55 (15,548/15,619) (99.43, 99.64)	99.53 (13,486/13,550) (99.40, 99.63)	99.62 (14,620/14,676) (99.50, 99.71)	99.60 (13,927/13,983) (99.48, 99.69)	99.50 (11,085/11,141) (99.35, 99.61)
Second ^b	99.58 (13,775/13,833) (99.46, 99.68)	99.62 (12,298/12,345) (99.49, 99.71)	99.60 (13,525/13,579) (99.48, 99.70)	99.61 (13,023/13,074) (99.49, 99.70)	99.56 (10,456/10,502) (99.42, 99.67)
Third ^c	99.47 (13,275/13,346) (99.33, 99.58)	99.41 (11,809/11,879) (99.26, 99.53)	99.58 (13,071/13,126) (99.46, 99.68)	99.60 (12,596/12,646) (99.48, 99.70)	99.44 (10,106/10,163) (99.27, 99.57)
Aggregate ^d	99.53 (42,598/42,798) (99.46, 99.59)	99.52 (37,593/37,774) (99.45, 99.59)	99.60 (41,216/41,381) (99.54, 99.66)	99.60 (39,546/39,703) (99.54, 99.66)	99.50 (31,647/31,806) (99.42, 99.57)
False-positive rate					

Screening round	Quintile 1 Estimate (n/N) (95% CI)	Quintile 2 Estimate (n/N) (95% CI)	Quintile 3 Estimate (n/N) (95% CI)	Quintile 4 Estimate (n/N) (95% CI)	Quintile 5 Estimate (n/N) (95% CI)
First ^a	0.45 (71/15,619) (0.36, 0.57)	0.47 (64/13,550) (0.37, 0.60)	0.38 (56/14,676) (0.29, 0.50)	0.40 (56/13,983) (0.31, 0.52)	0.50 (56/11,141) (0.39, 0.65)
Second ^b	0.42 (58/13,833) (0.32, 0.54)	0.38 (47/12,345) (0.29, 0.51)	0.40 (54/13,579) (0.30, 0.52)	0.39 (51/13,074) (0.30, 0.51)	0.44 (46/10,502) (0.33, 0.58)
Third ^c	0.53 (71/13,346) (0.42, 0.67)	0.59 (70/11,879) (0.47, 0.74)	0.42 (55/13,126) (0.32, 0.54)	0.40 (50/12,646) (0.30, 0.52)	0.56 (57/10,163) (0.43, 0.73)
Aggregate ^d	0.47 (200/42,798) (0.41, 0.54)	0.48 (181/37,774) (0.41, 0.55)	0.40 (165/41,381) (0.34, 0.46)	0.40 (157/39,703) (0.34, 0.46)	0.50 (159/31,806) (0.43, 0.58)
MCED cancer detection rate					
First ^a	0.59 (93/15,863) (0.48, 0.72)	0.57 (79/13,780) (0.46, 0.71)	0.54 (80/14,887) (0.43, 0.67)	0.63 (90/14,215) (0.52, 0.78)	0.68 (77/11,348) (0.54, 0.85)
Second ^b	0.38 (54/14,030) (0.30, 0.50)	0.41 (52/12,531) (0.32, 0.54)	0.43 (59/13,774) (0.33, 0.55)	0.40 (53/13,285) (0.31, 0.52)	0.40 (43/10,675) (0.30, 0.54)
Third ^c	0.44 (60/13,547) (0.34, 0.57)	0.39 (47/12,059) (0.29, 0.52)	0.43 (58/13,350) (0.34, 0.56)	0.39 (50/12,840) (0.30, 0.51)	0.40 (41/10,324) (0.29, 0.54)
Aggregate ^d	0.48 (207/43,440) (0.42, 0.55)	0.46 (178/38,370) (0.40, 0.54)	0.47 (197/42,011) (0.41, 0.54)	0.48 (193/40,340) (0.42, 0.55)	0.50 (161/32,347) (0.43, 0.58)
MCED cancer signal detection rate					
First ^a	1.03 (164/15,863) (0.89, 1.20)	1.04 (143/13,780) (0.88, 1.22)	0.91 (136/14,887) (0.77, 1.08)	1.03 (146/14,215) (0.87, 1.21)	1.17 (133/11,348) (0.99, 1.39)
Second ^b	0.80 (112/14,030) (0.66, 0.96)	0.79 (99/12,531) (0.65, 0.96)	0.82 (113/13,774) (0.68, 0.99)	0.78 (104/13,285) (0.65, 0.95)	0.83 (89/10,675) (0.68, 1.02)

Screening round	Quintile 1 Estimate (n/N) (95% CI)	Quintile 2 Estimate (n/N) (95% CI)	Quintile 3 Estimate (n/N) (95% CI)	Quintile 4 Estimate (n/N) (95% CI)	Quintile 5 Estimate (n/N) (95% CI)
Third ^c	0.97 (131/13,547) (0.82, 1.15)	0.97 (117/12,059) (0.81, 1.16)	0.85 (113/13,350) (0.70, 1.02)	0.78 (100/12,840) (0.64, 0.95)	0.95 (98/10,324) (0.78, 1.16)
Aggregate ^d	0.94 (407/43,440) (0.85, 1.03)	0.94 (359/38,370) (0.84, 1.04)	0.86 (362/42,011) (0.78, 0.95)	0.87 (350/40,340) (0.78, 0.96)	0.99 (320/32,347) (0.89, 1.10)

^a232 participants with missing subgroup values are not included.

^b203 participants with missing subgroup values are not included.

^c203 participants with missing subgroup values are not included.

^dScreening episodes from participants with missing subgroup values are not included.

MCED, multi-cancer early detection; IMD, Index of Multiple Deprivation; NPV, negative predictive value; PPV, positive predictive value.

Supplementary Table S8. Performance Metrics by Subgroup: Education.

Screening round	School at or before the age of 15 Estimate (n/N) (95% CI)	CSEs, O-levels or equivalent Estimate (n/N) (95% CI)	A-levels or equivalent Estimate (n/N) (95% CI)	Further education without a degree Estimate (n/N) (95% CI)	Bachelor's degree or equivalent Estimate (n/N) (95% CI)	Further degree e.g., Masters or PhD Estimate (n/N) (95% CI)
PPV						
First ^a	56.2 (91/162) (48.5, 63.6)	59.1 (94/159) (51.4, 66.5)	60.3 (35/58) (47.5, 71.9)	57.3 (94/164) (49.7, 64.6)	57.3 (67/117) (48.2, 65.9)	61.3 (38/62) (48.8, 72.4)
Second ^b	56.5 (65/115) (47.4, 65.2)	51.8 (57/110) (42.6, 60.9)	50.8 (31/61) (38.6, 62.9)	41.7 (48/115) (33.1, 50.9)	51.3 (40/78) (40.4, 62.1)	51.3 (20/39) (36.2, 66.1)
Third ^c	53.5 (61/114) (44.4, 62.4)	45.6 (62/136) (37.5, 54.0)	46.3 (25/54) (33.7, 59.4)	42.1 (59/140) (34.3, 50.4)	43.2 (32/74) (32.6, 54.6)	42.9 (18/42) (29.1, 57.8)
Aggregate ^d	55.5 (217/391) (50.5, 60.3)	52.6 (213/405) (47.7, 57.4)	52.6 (91/173) (45.2, 59.9)	48.0 (201/419) (43.2, 52.8)	51.7 (139/269) (45.7, 57.6)	53.1 (76/143) (45.0, 61.1)
NPV						
First ^a	98.91 (12,240/12,375) (98.71, 99.08)	99.11 (18,724/18,892) (98.97, 99.23)	98.93 (6314/6382) (98.65, 99.16)	98.95 (14,294/14,446) (98.77, 99.10)	98.90 (11,590/11,719) (98.69, 99.07)	99.02 (5648/5704) (98.73, 99.24)
Second ^b	98.52 (10,951/11,116) (98.27, 98.72)	99.10 (17,244/17,401) (98.95, 99.23)	98.78 (5763/5834) (98.47, 99.03)	98.98 (13,265/13,402) (98.79, 99.13)	99.02 (10,776/10,883) (98.81, 99.19)	98.84 (5194/5255) (98.51, 99.10)
Third ^c	98.44 (10,506/10,673)	99.08 (16,675/16,829)	98.79 (5549/5617)	98.86 (12,795/12,942)	98.99 (10,436/10,543)	98.84 (5016/5075)

Screening round	School at or before the age of 15 Estimate (n/N) (95% CI)	CSEs, O-levels or equivalent Estimate (n/N) (95% CI)	A-levels or equivalent Estimate (n/N) (95% CI)	Further education without a degree Estimate (n/N) (95% CI)	Bachelor's degree or equivalent Estimate (n/N) (95% CI)	Further degree e.g., Masters or PhD Estimate (n/N) (95% CI)
	(98.18, 98.65)	(98.93, 99.22)	(98.47, 99.04)	(98.67, 99.03)	(98.78, 99.16)	(98.50, 99.10)
Aggregate ^d	98.63 (33,697/34,164) (98.50, 98.75)	99.10 (52,643/53,122) (99.01, 99.18)	98.84 (17,626/17,833) (98.67, 98.99)	98.93 (40,354/40,790) (98.83, 99.03)	98.97 (32,802/33,145) (98.85, 99.07)	98.9 (15,858/16,034) (98.73, 99.05)
Episode sensitivity						
First ^a	40.3 (91/226) (34.1, 46.8)	35.9 (94/262) (30.3, 41.9)	34.0 (35/103) (25.6, 43.6)	38.2 (94/246) (32.4, 44.4)	34.2 (67/196) (27.9, 41.1)	40.4 (38/94) (31.1, 50.5)
Second ^b	28.3 (65/230) (22.8, 34.4)	26.6 (57/214) (21.2, 32.9)	30.4 (31/102) (22.3, 39.9)	25.9 (48/185) (20.2, 32.7)	27.2 (40/147) (20.7, 34.9)	24.7 (20/81) (16.6, 35.1)
Third ^c	26.8 (61/228) (21.4, 32.9)	28.7 (62/216) (23.1, 35.1)	26.9 (25/93) (18.9, 36.7)	28.6 (59/206) (22.9, 35.2)	23.0 (32/139) (16.8, 30.7)	23.4 (18/77) (15.3, 34.0)
Aggregate ^d	31.7 (217/684) (28.3, 35.3)	30.8 (213/692) (27.5, 34.3)	30.5 (91/298) (25.6, 36.0)	31.6 (201/637) (28.1, 35.3)	28.8 (139/482) (25.0, 33.0)	30.2 (76/252) (24.8, 36.1)
Specificity						
First ^a	99.42 (12,240/12,311) (99.27, 99.54)	99.65 (18,724/18,789) (99.56, 99.73)	99.64 (6314/6337) (99.46, 99.76)	99.51 (14,294/14,364) (99.38, 99.61)	99.57 (11,590/11,640) (99.43, 99.67)	99.58 (5648/5672) (99.37, 99.72)
Second ^b	99.55 (10,951/11,001)	99.69 (17,244/17,297)	99.48 (5763/5793)	99.50 (13,265/13,332)	99.65 (10,776/10,814)	99.64 (5194/5213)

Screening round	School at or before the age of 15 Estimate (n/N) (95% CI)	CSEs, O-levels or equivalent Estimate (n/N) (95% CI)	A-levels or equivalent Estimate (n/N) (95% CI)	Further education without a degree Estimate (n/N) (95% CI)	Bachelor's degree or equivalent Estimate (n/N) (95% CI)	Further degree e.g., Masters or PhD Estimate (n/N) (95% CI)
	(99.40, 99.66)	(99.60, 99.77)	(99.26, 99.64)	(99.36, 99.60)	(99.52, 99.74)	(99.43, 99.77)
Third ^c	99.50 (10,506/10,559) (99.34, 99.62)	99.56 (16,675/16,749) (99.45, 99.65)	99.48 (5549/5578) (99.25, 99.64)	99.37 (12,795/12,876) (99.22, 99.49)	99.60 (10,436/10,478) (99.46, 99.70)	99.52 (5016/5040) (99.29, 99.68)
Aggregate ^d	99.49 (33,697/33,871) (99.40, 99.56)	99.64 (52,643/52,835) (99.58, 99.68)	99.54 (17,626/17,708) (99.43, 99.63)	99.46 (40,354/40,572) (99.39, 99.53)	99.61 (32,802/32,932) (99.53, 99.67)	99.58 (15,858/15,925) (99.47, 99.67)
False-positive rate						
First ^a	0.58 (71/12,311) (0.46, 0.73)	0.35 (65/18,789) (0.27, 0.44)	0.36 (23/6337) (0.24, 0.54)	0.49 (70/14,364) (0.39, 0.62)	0.43 (50/11,640) (0.33, 0.57)	0.42 (24/5672) (0.28, 0.63)
Second ^b	0.45 (50/11,001) (0.34, 0.60)	0.31 (53/17,297) (0.23, 0.40)	0.52 (30/5793) (0.36, 0.74)	0.50 (67/13,332) (0.40, 0.64)	0.35 (38/10,814) (0.26, 0.48)	0.36 (19/5213) (0.23, 0.57)
Third ^c	0.50 (53/10,559) (0.38, 0.66)	0.44 (74/16,749) (0.35, 0.55)	0.52 (29/5578) (0.36, 0.75)	0.63 (81/12,876) (0.51, 0.78)	0.40 (42/10,478) (0.30, 0.54)	0.48 (24/5040) (0.32, 0.71)
Aggregate ^d	0.51 (174/33,871) (0.44, 0.60)	0.36 (192/52,835) (0.32, 0.42)	0.46 (82/17,708) (0.37, 0.57)	0.54 (218/40,572) (0.47, 0.61)	0.39 (130/32,932) (0.33, 0.47)	0.42 (67/15,925) (0.33, 0.53)

Screening round	School at or before the age of 15 Estimate (n/N) (95% CI)	CSEs, O-levels or equivalent Estimate (n/N) (95% CI)	A-levels or equivalent Estimate (n/N) (95% CI)	Further education without a degree Estimate (n/N) (95% CI)	Bachelor's degree or equivalent Estimate (n/N) (95% CI)	Further degree e.g., Masters or PhD Estimate (n/N) (95% CI)
MCED cancer detection rate						
First ^a	0.73 (91/12,537) (0.59, 0.89)	0.49 (94/19,051) (0.40, 0.60)	0.54 (35/6440) (0.39, 0.75)	0.64 (94/14,610) (0.53, 0.79)	0.57 (67/11,836) (0.45, 0.72)	0.66 (38/5766) (0.48, 0.90)
Second ^b	0.580 (65/11,231) (0.45, 0.74)	0.33 (57/17,511) (0.25, 0.42)	0.53 (31/5,895) (0.37, 0.75)	0.36 (48/13,517) (0.27, 0.47)	0.36 (40/10,961) (0.27, 0.50)	0.38 (20/5,294) (0.24, 0.58)
Third ^c	0.57 (61/10,787) (0.44, 0.73)	0.37 (62/16,965) (0.29, 0.47)	0.44 (25/5671) (0.30, 0.65)	0.45 (59/13,082) (0.35, 0.58)	0.30 (32/10,617) (0.21, 0.43)	0.35 (18/5117) (0.22, 0.56)
Aggregate ^d	0.63 (217/34,555) (0.55, 0.72)	0.40 (213/53,527) (0.35, 0.45)	0.51 (91/18,006) (0.41, 0.62)	0.49 (201/41,209) (0.42, 0.56)	0.42 (139/33,414) (0.35, 0.49)	0.47 (76/16,177) (0.38, 0.59)
MCED cancer signal detection rate						
First ^a	1.29 (162/12,537) (1.11, 1.51)	0.83 (159/19,051) (0.71, 0.97)	0.90 (58/6,440) (0.70, 1.16)	1.12 (164/14,610) (0.96, 1.31)	0.99 (117/11,836) (0.83, 1.18)	1.08 (62/5,766) (0.84, 1.38)
Second ^b	1.02 (115/11,231) (0.85, 1.23)	0.63 (110/17,511) (0.52, 0.76)	1.03 (61/5895) (0.81, 1.33)	0.85 (115/13,517) (0.71, 1.02)	0.71 (78/10,961) (0.57, 0.89)	0.74 (39/5294) (0.54, 1.01)

Screening round	School at or before the age of 15 Estimate (n/N) (95% CI)	CSEs, O-levels or equivalent Estimate (n/N) (95% CI)	A-levels or equivalent Estimate (n/N) (95% CI)	Further education without a degree Estimate (n/N) (95% CI)	Bachelor's degree or equivalent Estimate (n/N) (95% CI)	Further degree e.g., Masters or PhD Estimate (n/N) (95% CI)
Third ^c	1.06 (114/10,787) (0.88, 1.27)	0.80 (136/16,965) (0.68, 0.95)	0.95 (54/5671) (0.73, 1.24)	1.07 (140/13,082) (0.91, 1.26)	0.70 (74/10,617) (0.56, 0.87)	0.82 (42/5117) (0.61, 1.11)
Aggregate ^d	1.13 (391/34,555) (1.03, 1.25)	0.76 (405/53,527) (0.69, 0.83)	0.96 (173/18,006) (0.83, 1.11)	1.02 (419/41,209) (0.92, 1.12)	0.81 (269/33,414) (0.71, 0.91)	0.88 (143/16,177) (0.75, 1.04)

^a85 participants with missing subgroup values are not included.

^b89 participants with missing subgroup values are not included.

^c84 participants with missing subgroup values are not included.

^dScreening episodes from participants with missing subgroup values are not included.

A-levels, advanced levels; CSE, certificate of secondary education; MCED, multi-cancer early detection; NPV, negative predictive value; O-levels, ordinary levels; PPV, positive predictive value.

Supplementary Table S9. PPV by CSO Prediction by Round and in Aggregate.

MCED CSO1 prediction	Positive MCED result, cancer diagnosis, n (%)	Positive MCED result, no cancer diagnosis, n (%)	PPV,^a % (n/N) (95% CI)
First screening round (n=722)			
Total, n	419	303	
Anus	2 (0.5)	3 (1.0)	40.0 (2/5) (11.8, 76.9)
Bladder, Urothelial Tract	2 (0.5)	2 (0.7)	2/4
Bone and Soft Tissue	1 (0.2)	2 (0.7)	1/3
Breast	26 (6.2)	29 (9.6)	47.3 (26/55) (34.7, 60.2)
Cervix	0	1 (0.3)	0/1
Colon, Rectum	84 (20.0)	79 (26.1)	51.5 (84/163) (43.9, 59.1)
Head and Neck	24 (5.7)	17 (5.6)	58.5 (24/41) (43.4, 72.2)
Kidney	10 (2.4)	2 (0.7)	83.3 (10/12) (55.2, 95.3)
Liver, Bile Duct	13 (3.1)	6 (2.0)	68.4 (13/19) (46.0, 84.6)
Lung	53 (12.6)	28 (9.2)	65.4 (53/81) (54.6, 74.9)
Lymphoid Lineage	57 (13.6)	67 (22.1)	46.0 (57/124) (37.4, 54.7)
Melanocytic Lineage	2 (0.5)	0	2/2
Neuroendocrine Cells of the Lung or Other Organs	8 (1.9)	1 (0.3)	88.9 (8/9) (56.5, 98.0)
Ovary	15 (3.6)	1 (0.3)	93.8 (15/16) (71.7, 98.9)

MCED CSO1 prediction	Positive MCED result, cancer diagnosis, n (%)	Positive MCED result, no cancer diagnosis, n (%)	PPV,^a % (n/N) (95% CI)
Pancreas, Gallbladder	23 (5.5)	7 (2.3)	76.7 (23/30) (59.1, 88.2)
Plasma Cell Lineage	24 (5.7)	20 (6.6)	54.5 (24/44) (40.1, 68.3)
Prostate	39 (9.3)	22 (7.3)	63.9 (39/61) (51.4, 74.8)
Stomach, Oesophagus	27 (6.4)	13 (4.3)	67.5 (27/40) (52.0, 79.9)
Thyroid Gland	0	1 (0.3)	0/1
Uterus	9 (2.1)	2 (0.7)	81.8 (9/11) (52.3, 94.9)
Second screening round (n=518)			
Total, n	261	257	
Anus	3 (1.1)	2 (0.8)	60.0 (3/5) (23.1, 88.2)
Bladder, Urothelial Tract	8 (3.1)	1 (0.4)	88.9 (8/9) (56.5, 98.0)
Bone and Soft Tissue	0	2 (0.8)	0/2
Breast	18 (6.9)	25 (9.7)	41.9 (18/43) (28.4, 56.7)
Cervix	1 (0.4)	0	1/1
Colon, Rectum	58 (22.2)	69 (26.8)	45.7 (58/127) (37.3, 54.3)
Head and Neck	11 (4.2)	14 (5.4)	44.0 (11/25) (26.7, 62.9)
Kidney	0	3 (1.2)	0/3
Liver, Bile Duct	5 (1.9)	2 (0.8)	71.4 (5/7) (35.9, 91.8)
Lung	33 (12.6)	25 (9.7)	56.9 (33/58) (44.1, 68.8)

MCED CSO1 prediction	Positive MCED result, cancer diagnosis, n (%)	Positive MCED result, no cancer diagnosis, n (%)	PPV,^a % (n/N) (95% CI)
Lymphoid Lineage	29 (11.1)	41 (16.0)	41.4 (29/70) (30.6, 53.1)
Melanocytic Lineage	1 (0.4)	0	1/1
Neuroendocrine Cells of Lung or Other Organs	8 (3.1)	2 (0.8)	80.0 (8/10) (49.0, 94.3)
Ovary	6 (2.3)	0	100 (6/6) (61.0, 100)
Pancreas, Gallbladder	15 (5.7)	12 (4.7)	55.6 (15/27) (37.3, 72.4)
Plasma Cell Lineage	10 (3.8)	17 (6.6)	37.0 (10/27) (21.5, 55.8)
Prostate	30 (11.5)	23 (8.9)	56.6 (30/53) (43.3, 69.0)
Stomach, Oesophagus	18 (6.9)	12 (4.7)	60.0 (18/30) (42.3, 75.4)
Uterus	7 (2.7)	7 (2.7)	50.0 (7/14) (26.8, 73.2)
Third screening round (n=561)			
Total, n	257	304	
Anus	1 (0.4)	2 (0.7)	1/3
Bladder, Urothelial Tract	4 (1.6)	2 (0.7)	66.7 (4/6) (30.0, 90.3)
Breast	19 (7.4)	26 (8.6)	42.2 (19/45) (29.0, 56.7)
Cervix	0	1 (0.3)	0/1
Colon, Rectum	49 (19.1)	69 (22.7)	41.5 (49/118) (33.0, 50.5)
Head and Neck	13 (5.1)	17 (5.6)	43.3 (13/30) (27.4, 60.8)

MCED CSO1 prediction	Positive MCED result, cancer diagnosis, n (%)	Positive MCED result, no cancer diagnosis, n (%)	PPV,^a % (n/N) (95% CI)
Kidney	4 (1.6)	3 (1.0)	57.1 (4/7) (25.0, 84.2)
Liver, Bile Duct	12 (4.7)	9 (3.0)	57.1 (12/21) (36.5, 75.5)
Lung	37 (14.4)	31 (10.2)	54.4 (37/68) (42.7, 65.7)
Lymphoid Lineage	26 (10.1)	59 (19.4)	30.6 (26/85) (21.8, 41.0)
Melanocytic Lineage	2 (0.8)	2 (0.7)	2/4
Neuroendocrine Cells of Lung or Other Organs	8 (3.1)	2 (0.7)	80.0 (8/10) (49.0, 94.3)
Ovary	7 (2.7)	1 (0.3)	87.5 (7/8) (52.9, 97.8)
Pancreas, Gallbladder	16 (6.2)	11 (3.6)	59.3 (16/27) (40.7, 75.5)
Plasma Cell Lineage	13 (5.1)	18 (5.9)	41.9 (13/31) (26.4, 59.2)
Prostate	20 (7.8)	23 (7.6)	46.5 (20/43) (32.5, 61.1)
Stomach, Oesophagus	19 (7.4)	10 (3.3)	65.5 (19/29) (47.3, 80.1)
Uterus	7 (2.7)	18 (5.9)	28.0 (7/25) (14.3, 47.6)
Aggregate (N=1801)			
Total, n	937	864	
Anus	6 (0.6)	7 (0.8)	46.2 (6/13) (23.2, 70.9)
Bladder, Urothelial Tract	14 (1.5)	5 (0.6)	73.7 (14/19) (51.2, 88.2)

MCED CSO1 prediction	Positive MCED result, cancer diagnosis, n (%)	Positive MCED result, no cancer diagnosis, n (%)	PPV,^a % (n/N) (95% CI)
Bone and Soft Tissue	1 (0.1)	4 (0.5)	20.0 (1/5) (3.6, 62.4)
Breast	63 (6.7)	80 (9.3)	44.1 (63/143) (36.2, 52.2)
Cervix	1 (0.1)	2 (0.2)	1/3
Colon, Rectum	191 (20.4)	217 (25.1)	46.8 (191/408) (42.0, 51.7)
Head and Neck	48 (5.1)	48 (5.6)	50.0 (48/96) (40.2, 59.8)
Kidney	14 (1.5)	8 (0.9)	63.6 (14/22) (43.0, 80.3)
Liver, Bile Duct	30 (3.2)	17 (2.0)	63.8 (30/47) (49.5, 76.0)
Lung	123 (13.1)	84 (9.7)	59.4 (123/207) (52.6, 65.9)
Lymphoid Lineage	112 (12.0)	167 (19.3)	40.1 (112/279) (34.6, 46.0)
Melanocytic Lineage	5 (0.5)	2 (0.2)	71.4 (5/7) (35.9, 91.8)
Neuroendocrine Cells of Lung or other Organs	24 (2.6)	5 (0.6)	82.8 (24/29) (65.5, 92.4)
Ovary	28 (3.0)	2 (0.2)	93.3 (28/30) (78.7, 98.2)
Pancreas, Gallbladder	54 (5.8)	30 (3.5)	64.3 (54/84) (53.6, 73.7)
Plasma Cell Lineage	47 (5.0)	55 (6.4)	46.1 (47/102) (36.7, 55.7)
Prostate	89 (9.5)	68 (7.9)	56.7 (89/157) (48.9, 64.2)
Stomach, Oesophagus	64 (6.8)	35 (4.1)	64.6 (64/99) (54.8, 73.4)

MCED CSO1 prediction	Positive MCED result, cancer diagnosis, n (%)	Positive MCED result, no cancer diagnosis, n (%)	PPV,^a % (n/N) (95% CI)
Thyroid Gland	0	1 (0.1)	0/1
Uterus	23 (2.5)	27 (3.1)	46.0 (23/50) (33.0, 59.6)

^aPPV is not estimated for CSOs with less than 5 cases.

CSO, cancer signal origin; MCED, multi-cancer detection; PPV, positive predictive value.

Supplementary Table S10. Characteristics of First Primary Cancers in Participants.

Cancer type diagnosed	Stage, ^a n (%)						Total, n (%)
	I	II	III	IV	Unstageable ^b	Missing	
First screening round							
Participants with positive MCED test results and cancer diagnosis							
Total	88 (21.0)	78 (18.6)	123 (29.4)	103 (24.6)	4 (1.0)	23 (5.5)	419
Anus	0	0	2 (66.7)	1 (33.3)	0	0	3 (0.7)
Bladder	1 (50.0)	1 (50.0)	0	0	0	0	2 (0.5)
Breast	6 (20.7)	13 (44.8)	5 (17.2)	4 (13.8)	0	1 (3.4)	29 (6.9)
Cervix	0	0	0	1 (100)	0	0	1 (0.2)
Colon/Rectum	21 (24.7)	22 (25.9)	25 (29.4)	15 (17.6)	0	2 (2.4)	85 (20.3)
Gallbladder	0	2 (40.0)	2 (40.0)	1 (20.0)	0	0	5 (1.2)
Head and Neck	10 (62.5)	1 (6.2)	4 (25.0)	1 (6.2)	0	0	16 (3.8)
Kidney	0	3 (33.3)	2 (22.2)	3 (33.3)	0	1 (11.1)	9 (2.1)
Liver/Bile-duct	4 (30.8)	5 (38.5)	1 (7.7)	3 (23.1)	0	0	13 (3.1)
Lung	4 (7.5)	4 (7.5)	24 (45.3)	21 (39.6)	0	0	53 (12.6)
Lymphoid Leukaemia	10 (71.4)	2 (14.3)	0	0	0	2 (14.3)	14 (3.3)
Lymphoma	6 (18.2)	4 (12.1)	12 (36.4)	11 (33.3)	0	0	33 (7.9)

Cancer type diagnosed	Stage, ^a n (%)						Total, n (%)
	I	II	III	IV	Unstageable ^b	Missing	
Melanoma	1 (33.3)	0	1 (33.3)	1 (33.3)	0	0	3 (0.7)
Myeloid Neoplasm	0	0	0	0	1 (100)	0	1 (0.2)
Oesophagus	1 (5.0)	2 (10.0)	12 (60.0)	4 (20.0)	0	1 (5.0)	20 (4.8)
Ovary	2 (10.5)	2 (10.5)	13 (68.4)	2 (10.5)	0	0	19 (4.5)
Pancreas	2 (11.1)	2 (11.1)	2 (11.1)	11 (61.1)	0	1 (5.6)	18 (4.3)
Plasma Cell Neoplasm	4 (19.0)	3 (14.3)	0	0	0	14 (66.7)	21 (5.0)
Prostate	11 (22.9)	3 (6.2)	16 (33.3)	18 (37.5)	0	0	48 (11.5)
Sarcoma	0	0	0	1 (50.0)	1 (50.0)	0	2 (0.5)
Stomach	0	5 (55.6)	2 (22.2)	2 (22.2)	0	0	9 (2.1)
Thyroid	0	1 (100)	0	0	0	0	1 (0.2)
Uterus	3 (42.9)	2 (28.6)	0	2 (28.6)	0	0	7 (1.7)
Other ^c	2 (50.0)	0	0	0	1 (25.0)	1 (25.0)	4 (1.0)
Multiple cancers	0	1 (100)	0	0	0	0	1 (0.2)
NCRAS Cancer of Unknown Primary ^d	0	0	0	1 (50.0)	1 (50.0)	0	2 (0.5)

Cancer type diagnosed	Stage, ^a n (%)						Total, n (%)
	I	II	III	IV	Unstageable ^b	Missing	
Participants with negative MCED test results whose cancer diagnosis was triggered by NHS cancer screening							
Total	51 (69.9)	18 (24.7)	2 (2.7)	2 (2.7)	0	0	73
Breast	48 (72.7)	17 (25.8)	1 (1.5)	0	0	0	66 (90.4)
Colon/Rectum	3 (50.0)	1 (16.7)	1 (16.7)	1 (16.7)	0	0	6 (8.2)
Lung	0	0	0	1 (100)	0	0	1 (1.4)
Participants with negative MCED test results whose cancer diagnosis was not triggered by NHS cancer screening							
Total	294 (46.3)	115 (18.1)	120 (18.9)	54 (8.5)	34 (5.4)	18 (2.8)	635
Anus	0	0	2 (100)	0	0	0	2 (0.3)
Bladder	8 (57.1)	4 (28.6)	1 (7.1)	1 (7.1)	0	0	14 (2.2)
Breast	20 (35.1)	31 (54.4)	3 (5.3)	2 (3.5)	0	1 (1.8)	57 (9.0)
Cervix	0	1 (100)	0	0	0	0	1 (0.2)
Colon/Rectum	20 (55.6)	5 (13.9)	6 (16.7)	5 (13.9)	0	0	36 (5.7)
Gallbladder	1 (25.0)	1 (25.0)	1 (25.0)	0	0	1 (25.0)	4 (0.6)
Head and Neck	5 (45.5)	2 (18.2)	2 (18.2)	2 (18.2)	0	0	11 (1.7)
Kidney	10 (45.5)	2 (9.1)	8 (36.4)	2 (9.1)	0	0	22 (3.5)
Liver/Bile-duct	1 (33.3)	1 (33.3)	0	1 (33.3)	0	0	3 (0.5)
Lung	12 (42.9)	2 (7.1)	5 (17.9)	9 (32.1)	0	0	28 (4.4)

Cancer type diagnosed	Stage, ^a n (%)						Total, n (%)
	I	II	III	IV	Unstageable ^b	Missing	
Lymphoid Leukaemia	10 (66.7)	3 (20.0)	2 (13.3)	0	0	0	15 (2.4)
Lymphoma	8 (40.0)	0	5 (25.0)	7 (35.0)	0	0	20 (3.1)
Melanoma	33 (67.3)	9 (18.4)	4 (8.2)	0	0	3 (6.1)	49 (7.7)
Myeloid Neoplasm	0	0	0	0	18 (100)	0	18 (2.8)
Oesophagus	0	1 (14.3)	3 (42.9)	3 (42.9)	0	0	7 (1.1)
Ovary	2 (25.0)	0	5 (62.5)	1 (12.5)	0	0	8 (1.3)
Pancreas	3 (20.0)	2 (13.3)	2 (13.3)	8 (53.3)	0	0	15 (2.4)
Plasma Cell Neoplasm	2 (20.0)	2 (20.0)	0	0	0	6 (60.0)	10 (1.6)
Prostate	124 (52.1)	46 (19.3)	55 (23.1)	9 (3.8)	0	4 (1.7)	238 (37.5)
Sarcoma	1 (14.3)	1 (14.3)	4 (57.1)	0	0	1 (14.3)	7 (1.1)
Stomach	0	1 (20.0)	1 (20.0)	3 (60.0)	0	0	5 (0.8)
Thyroid	4 (100)	0	0	0	0	0	4 (0.6)
Urothelial Tract	0	0	2 (100)	0	0	0	2 (0.3)
Uterus	26 (96.3)	0	1 (3.7)	0	0	0	27 (4.3)
Other ^e	4 (13.3)	1 (3.3)	8 (26.7)	1 (3.3)	14 (46.7)	2 (6.7)	30 (4.7)
NCRAS Cancer of	0	0	0	0	2 (100)	0	2 (0.3)

Cancer type diagnosed	Stage, ^a n (%)						Total, n (%)
	I	II	III	IV	Unstageable ^b	Missing	
Unknown Primary ^d							
Second screening round							
Participants with positive MCED test results and cancer diagnosis							
Total	56 (21.5)	49 (18.8)	75 (28.7)	65 (24.9)	2 (0.8)	14 (5.4)	261
Anus	2 (66.7)	0	1 (33.3)	0	0	0	3 (1.1)
Bladder	2 (66.7)	0	1 (33.3)	0	0	0	3 (1.1)
Breast	1 (6.7)	10 (66.7)	3 (20.0)	1 (6.7)	0	0	15 (5.7)
Cervix	1 (100)	0	0	0	0	0	1 (0.4)
Colon/Rectum	20 (35.7)	14 (25.0)	16 (28.6)	6 (10.7)	0	0	56 (21.5)
Gallbladder	0	1 (33.3)	0	2 (66.7)	0	0	3 (1.1)
Head and Neck	5 (62.5)	2 (25.0)	1 (12.5)	0	0	0	8 (3.1)
Kidney	0	0	1 (100)	0	0	0	1 (0.4)
Liver/Bile-duct	2 (25.0)	3 (37.5)	3 (37.5)	0	0	0	8 (3.1)
Lung	5 (13.5)	4 (10.8)	16 (43.2)	11 (29.7)	0	1 (2.7)	37 (14.2)
Lymphoid Leukaemia	5 (71.4)	1 (14.3)	0	0	0	1 (14.3)	7 (2.7)
Lymphoma	0	4 (21.1)	5 (26.3)	9 (47.4)	0	1 (5.3)	19 (7.3)

Cancer type diagnosed	Stage, ^a n (%)						Total, n (%)
	I	II	III	IV	Unstageable ^b	Missing	
Melanoma	0	0	0	1 (100)	0	0	1 (0.4)
Oesophagus	1 (10.0)	3 (30.0)	4 (40.0)	2 (20.0)	0	0	10 (3.8)
Ovary	1 (16.7)	0	2 (33.3)	3 (50.0)	0	0	6 (2.3)
Pancreas	0	1 (10.0)	2 (20.0)	7 (70.0)	0	0	10 (3.8)
Plasma Cell Neoplasm	0	1 (10.0)	0	0	0	9 (90.0)	10 (3.8)
Prostate	3 (8.6)	4 (11.4)	11 (31.4)	16 (45.7)	0	1 (2.9)	35 (13.4)
Sarcoma	0	0	0	0	0	1 (100)	1 (0.4)
Stomach	1 (16.7)	0	2 (33.3)	3 (50.0)	0	0	6 (2.3)
Urothelial Tract	0	0	1 (33.3)	2 (66.7)	0	0	3 (1.1)
Uterus	3 (50.0)	1 (16.7)	2 (33.3)	0	0	0	6 (2.3)
Other ^f	2 (25.0)	0	4 (50.0)	2 (25.0)	0	0	8 (3.1)
Multiple cancers	2 (100)	0	0	0	0	0	2 (0.8)
NCRAS Cancer of Unknown Primary ^d	0	0	0	0	2 (100)	0	2 (0.8)
Participants with negative MCED test results whose cancer diagnosis was triggered by NHS cancer screening							
Total	33 (58.9)	18 (32.1)	3 (5.4)	1 (1.8)	0	1 (1.8)	56

Cancer type diagnosed	Stage, ^a n (%)						Total, n (%)
	I	II	III	IV	Unstageable ^b	Missing	
Breast	24 (58.5)	15 (36.6)	1 (2.4)	0	0	1 (2.4)	41 (73.2)
Cervix	0	1 (100)	0	0	0	0	1 (1.8)
Colon/Rectum	7 (63.6)	2 (18.2)	1 (9.1)	1 (9.1)	0	0	11 (19.6)
Lung	2 (66.7)	0	1 (33.3)	0	0	0	3 (5.4)
Participants with negative MCED test results whose cancer diagnosis was not triggered by NHS cancer screening							
Total ⁹	304 (47.1)	107 (16.6)	137 (21.2)	50 (7.7)	36 (5.6)	11 (1.7)	646
Anus	1 (100)	0	0	0	0	0	1 (0.2)
Bladder	7 (43.8)	3 (18.8)	5 (31.2)	0	0	1 (6.2)	16 (2.5)
Breast	24 (42.9)	27 (48.2)	2 (3.6)	3 (5.4)	0	0	56 (8.7)
Colon/Rectum	16 (42.1)	6 (15.8)	12 (31.6)	4 (10.5)	0	0	38 (5.9)
Gallbladder	0	1 (100)	0	0	0	0	1 (0.2)
Head and Neck	5 (33.3)	2 (13.3)	4 (26.7)	4 (26.7)	0	0	15 (2.3)
Kidney	9 (47.4)	3 (15.8)	3 (15.8)	3 (15.8)	0	1 (5.3)	19 (2.9)
Liver/Bile-duct	0	0	0	1 (100)	0	0	1 (0.2)
Lung	31 (58.5)	2 (3.8)	7 (13.2)	13 (24.5)	0	0	53 (8.2)
Lymphoid Leukaemia	7 (53.8)	0	0	0	4 (30.8)	2 (15.4)	13 (2.0)

Cancer type diagnosed	Stage, ^a n (%)						Total, n (%)
	I	II	III	IV	Unstageable ^b	Missing	
Lymphoma	6 (30.0)	1 (5.0)	7 (35.0)	5 (25.0)	0	1 (5.0)	20 (3.1)
Melanoma	30 (63.8)	11 (23.4)	6 (12.8)	0	0	0	47 (7.3)
Myeloid Neoplasm	0	0	0	0	16 (100)	0	16 (2.5)
Oesophagus	1 (20.0)	2 (40.0)	2 (40.0)	0	0	0	5 (0.8)
Ovary	2 (28.6)	0	5 (71.4)	0	0	0	7 (1.1)
Pancreas	2 (20.0)	3 (30.0)	0	5 (50.0)	0	0	10 (1.5)
Plasma Cell Neoplasm	3 (37.5)	1 (12.5)	0	0	0	4 (50.0)	8 (1.2)
Prostate	121 (49.6)	38 (15.6)	75 (30.7)	8 (3.3)	0	2 (0.8)	244 (37.8)
Sarcoma	3 (75.0)	1 (25.0)	0	0	0	0	4 (0.6)
Stomach	1 (25.0)	2 (50.0)	0	1 (25.0)	0	0	4 (0.6)
Thyroid	3 (42.9)	1 (14.3)	0	3 (42.9)	0	0	7 (1.1)
Urothelial Tract	3 (50.0)	1 (16.7)	2 (33.3)	0	0	0	6 (0.9)
Uterus	17 (81.0)	1 (4.8)	3 (14.3)	0	0	0	21 (3.3)
Other ^{g,h}	11 (36.7)	1 (3.3)	4 (13.3)	0	13 (43.3)	0	30 (4.6)
Multiple cancers	1 (100)	0	0	0	0	0	1 (0.2)
NCRAS	0	0	0	0	3 (100)	0	3 (0.5)

Cancer type diagnosed	Stage, ^a n (%)						Total, n (%)
	I	II	III	IV	Unstageable ^b	Missing	
Cancer of Unknown Primary ^d							
Third screening round							
Participants with positive MCED test results and cancer diagnosis							
Total	58 (22.6)	37 (14.4)	76 (29.6)	64 (24.9)	4 (1.6)	18 (7.0)	257
Anus	1 (100)	0	0	0	0	0	1 (0.4)
Bladder	2 (50.0)	2 (50.0)	0	0	0	0	4 (1.6)
Breast	3 (18.8)	6 (37.5)	3 (18.8)	4 (25.0)	0	0	16 (6.2)
Colon/Rectum	15 (28.8)	9 (17.3)	22 (42.3)	6 (11.5)	0	0	52 (20.2)
Gallbladder	0	1 (14.3)	2 (28.6)	4 (57.1)	0	0	7 (2.7)
Head and Neck	7 (63.6)	0	2 (18.2)	2 (18.2)	0	0	11 (4.3)
Kidney	1 (25.0)	0	2 (50.0)	0	0	1 (25.0)	4 (1.6)
Liver/Bile-duct	5 (38.5)	4 (30.8)	2 (15.4)	1 (7.7)	0	1 (7.7)	13 (5.1)
Lung	4 (9.5)	6 (14.3)	20 (47.6)	12 (28.6)	0	0	42 (16.3)
Lymphoid Leukaemia	4 (80.0)	0	0	0	1 (20.0)	0	5 (1.9)
Lymphoma	5 (25.0)	2 (10.0)	3 (15.0)	10 (50.0)	0	0	20 (7.8)

Cancer type diagnosed	Stage, ^a n (%)						Total, n (%)
	I	II	III	IV	Unstageable ^b	Missing	
Melanoma	1 (50.0)	0	0	1 (50.0)	0	0	2 (0.8)
Myeloid Neoplasm	0	0	0	0	1 (100)	0	1 (0.4)
Oesophagus	2 (15.4)	4 (30.8)	1 (7.7)	4 (30.8)	0	2 (15.4)	13 (5.1)
Ovary	3 (30.0)	1 (10.0)	2 (20.0)	4 (40.0)	0	0	10 (3.9)
Pancreas	0	1 (12.5)	2 (25.0)	5 (62.5)	0	0	8 (3.1)
Plasma Cell Neoplasm	0	0	0	0	0	13 (100)	13 (5.1)
Prostate	2 (9.1)	1 (4.5)	10 (45.5)	8 (36.4)	1 (4.5)	0	22 (8.6)
Stomach	0	0	3 (75.0)	1 (25.0)	0	0	4 (1.6)
Uterus	2 (40.0)	0	1 (20.0)	2 (40.0)	0	0	5 (1.9)
Other ⁱ	1 (33.3)	0	1 (33.3)	0	0	1 (33.3)	3 (1.2)
NCRAS Cancer of Unknown Primary ^d	0	0	0	0	1 (100)	0	1 (0.4)
Participants with negative MCED test results whose cancer diagnosis was triggered by NHS cancer screening							
Total	38 (61.3)	17 (27.4)	6 (9.7)	1 (1.6)	0	0	62
Breast	27 (62.8)	14 (32.6)	2 (4.7)	0	0	0	43 (69.4)
Cervix	1 (100)	0	0	0	0	0	1 (1.6)

Cancer type diagnosed	Stage, ^a n (%)						Total, n (%)
	I	II	III	IV	Unstageable ^b	Missing	
Colon/Rectum	5 (45.5)	3 (27.3)	3 (27.3)	0	0	0	11 (17.7)
Lung	5 (71.4)	0	1 (14.3)	1 (14.3)	0	0	7 (11.3)
Participants with negative MCED test results whose cancer diagnosis was not triggered by NHS cancer screening							
Total	292 (45.5)	126 (19.6)	106 (16.5)	59 (9.2)	39 (6.1)	20 (3.1)	642
Bladder	11 (78.6)	2 (14.3)	0	1 (7.1)	0	0	14 (2.2)
Breast	22 (42.3)	28 (53.8)	1 (1.9)	1 (1.9)	0	0	52 (8.1)
Colon/Rectum	16 (57.1)	4 (14.3)	4 (14.3)	3 (10.7)	0	1 (3.6)	28 (4.4)
Gallbladder	0	1 (33.3)	0	2 (66.7)	0	0	3 (0.5)
Head and Neck	4 (36.4)	3 (27.3)	2 (18.2)	2 (18.2)	0	0	11 (1.7)
Kidney	9 (60.0)	0	5 (33.3)	1 (6.7)	0	0	15 (2.3)
Lung	25 (55.6)	4 (8.9)	8 (17.8)	8 (17.8)	0	0	45 (7.0)
Lymphoid Leukaemia	3 (50.0)	1 (16.7)	0	0	1 (16.7)	1 (16.7)	6 (0.9)
Lymphoma	4 (17.4)	4 (17.4)	5 (21.7)	10 (43.5)	0	0	23 (3.6)
Melanoma	42 (71.2)	14 (23.7)	3 (5.1)	0	0	0	59 (9.2)
Myeloid Neoplasm	0	0	0	0	27 (100)	0	27 (4.2)
Oesophagus	2 (20.0)	2 (20.0)	3 (30.0)	1 (10.0)	0	2 (20.0)	10 (1.6)

Cancer type diagnosed	Stage, ^a n (%)						Total, n (%)
	I	II	III	IV	Unstageable ^b	Missing	
Ovary	2 (28.6)	1 (14.3)	3 (42.9)	1 (14.3)	0	0	7 (1.1)
Pancreas	2 (11.8)	4 (23.5)	3 (17.6)	8 (47.1)	0	0	17 (2.6)
Plasma Cell Neoplasm	1 (9.1)	1 (9.1)	0	0	0	9 (81.8)	11 (1.7)
Prostate	119 (49.8)	50 (20.9)	57 (23.8)	13 (5.4)	0	0	239 (37.2)
Sarcoma	3 (30.0)	1 (10.0)	4 (40.0)	0	0	2 (20.0)	10 (1.6)
Stomach	0	0	0	1 (100)	0	0	1 (0.2)
Thyroid	5 (62.5)	3 (37.5)	0	0	0	0	8 (1.2)
Urothelial Tract	0	1 (25.0)	1 (25.0)	1 (25.0)	0	1 (25.0)	4 (0.6)
Uterus	13 (76.5)	0	1 (5.9)	2 (11.8)	0	1 (5.9)	17 (2.6)
Other ^d	9 (28.1)	2 (6.2)	5 (15.6)	4 (12.5)	9 (28.1)	3 (9.4)	32 (5.0)
Multiple cancers	0	0	1 (100)	0	0	0	1 (0.2)
NCRAS Cancer of Unknown Primary ^d	0	0	0	0	2 (100)	0	2 (0.3)

For participants with multiple cancer diagnoses, cancer type and stage were based on the earliest diagnosed cancer only.

^aThe cancer type and stage are based on the earliest diagnosed cancer if a participant had multiple cancers. The stage distribution is calculated based on the total number of cancers per cancer type.

^bUnstageable = no valid staging system exists for the combination of topo/morpho codes. Binet stages are mapped as follows: A=I, B=II, C=III; Chang stages are mapped as follows: M0=I, M1=II, M2/3=III, M4=IV.

^cOther cancer types in this group include brain (n=1), germ cell (n=1), mesothelioma (n=1), Vulva (n=1).

^dNCRAS Cancer of Unknown Primary is defined as an invasive cancer with ICD-O-3 behaviour code 6 or 9; or an invasive cancer with behaviour code 3, topographical code C809R and unmapped cancer label.

^eOther cancer types in this group include brain (n=12), mesothelioma (n=6), small intestine (n = 4), vulva (n=3), ampulla of Vater (n = 1), eyelid (n=1), penis (n=1), thymus (n=1), trachea (n=1).

^fOther cancer types in this group include small intestine (n=4), mesothelioma (n=2), germ cell (n=1), penis (n=1).

^gOne stage 0 cancer was diagnosed and included in totals but not shown here. Sums of the columns for this row are therefore less than the total.

^hOther cancer types in this group include brain (n=11), mesothelioma (n=7), vulva (n=3), germ cell (n=2), small intestine (n=2), thymus (n=2), carotid body (n=1), skin cancer (n=1), vagina (n=1).

ⁱOther cancer types in this group include mesothelioma (n=1), vagina (n=1), vulva (n=1).

^jOther cancer types in this group include brain (n=8), mesothelioma (n=7), small intestine (n=6), skin cancer (n=3), adrenal (n=2), ampulla of Vater (n=2), penis (n=2), vulva (n=2).

MCED, multi-cancer early detection; NCRAS, National Cancer Registration and Analysis Service; NHS, National Health Service.

Supplementary Table S11. Distribution of MCED-Detected Cancers by AJCC Cancer Types.

Cancer type diagnosed	First screening round, n (%) (n^a=439)	Second screening round, n (%) (n^a=275)	Third screening round, n (%) (n^a=265)	Aggregate, n (%) (n^a=979)
Anus	3 (0.7)	3 (1.1)	1 (0.4)	7 (0.7)
Appendix Carcinoma	2 (0.5)	1 (0.4)	0	3 (0.3)
Brain and Spinal Cord	1 (0.2)	0	0	1 (0.1)
Breast	29 (6.6)	17 (6.2)	17 (6.4)	63 (6.4)
Cervix Uteri	1 (0.2)	1 (0.4)	0	2 (0.2)
Colon and Rectum	86 (19.6)	57 (20.7)	53 (20.0)	196 (20.0)
Corpus Uteri - Carcinoma and Carcinosarcoma	7 (1.6)	6 (2.2)	6 (2.3)	19 (1.9)
Distal Bile Duct	1 (0.2)	0	0	1 (0.1)
Exocrine Pancreas	19 (4.3)	10 (3.6)	8 (3.0)	37 (3.8)
Gallbladder	2 (0.5)	3 (1.1)	5 (1.9)	10 (1.0)
Hodgkin and Non-Hodgkin Lymphomas	45 (10.3)	26 (9.5)	23 (8.7)	94 (9.6)
HPV-Mediated (p16+) Oropharyngeal Cancer	15 (3.4)	6 (2.2)	9 (3.4)	30 (3.1)
Intrahepatic Bile Ducts	6 (1.4)	4 (1.5)	2 (0.8)	12 (1.2)
Kidney	10 (2.3)	1 (0.4)	4 (1.5)	15 (1.5)
Larynx	1 (0.2)	0	0	1 (0.1)
Leukaemia	1 (0.2)	0	2 (0.8)	3 (0.3)
Liver	7 (1.6)	5 (1.8)	11 (4.2)	23 (2.3)
Lung	57 (13.0)	37 (13.5)	42 (15.8)	136 (13.9)
Major Salivary Glands	0	1 (0.4)	0	1 (0.1)
Malignant Pleural Mesothelioma	1 (0.2)	2 (0.7)	1 (0.4)	4 (0.4)
Melanoma of the Skin	3 (0.7)	2 (0.7)	3 (1.1)	8 (0.8)

Cancer type diagnosed	First screening round, n (%) (n^a=439)	Second screening round, n (%) (n^a=275)	Third screening round, n (%) (n^a=265)	Aggregate, n (%) (n^a=979)
Neuroendocrine Tumours of the Jejunum and Ileum	0	1 (0.4)	0	1 (0.1)
Neuroendocrine Tumours of the Pancreas	1 (0.2)	0	0	1 (0.1)
Oesophagus and Oesophagogastric Junction	16 (3.6)	8 (2.9)	10 (3.8)	34 (3.5)
Oral Cavity	1 (0.2)	0	0	1 (0.1)
Oropharynx (p16-) and Hypopharynx	0	2 (0.7)	2 (0.8)	4 (0.4)
Ovary, Fallopian Tube, and Primary Peritoneal Carcinoma	19 (4.3)	6 (2.2)	10 (3.8)	35 (3.6)
Penis	0	1 (0.4)	0	1 (0.1)
Perihilar Bile Ducts	2 (0.5)	0	2 (0.8)	4 (0.4)
Plasma Cell Myeloma and Plasma Cell Disorders	24 (5.5)	10 (3.6)	14 (5.3)	48 (4.9)
Prostate	52 (11.8)	38 (13.8)	24 (9.1)	114 (11.6)
Renal Pelvis and Ureter	1 (0.2)	5 (1.8)	0	6 (0.6)
Small Intestine	0	3 (1.1)	0	3 (0.3)
Soft Tissue Sarcoma - Unusual Histologies and Sites	1 (0.2)	0	0	1 (0.1)
Soft Tissue Sarcoma of the Abdomen and Thoracic Visceral Organs	1 (0.2)	0	0	1 (0.1)
Stomach	8 (1.8)	5 (1.8)	2 (0.8)	15 (1.5)
Testis	1 (0.2)	1 (0.4)	1 (0.4)	3 (0.3)

Cancer type diagnosed	First screening round, n (%) (n^a=439)	Second screening round, n (%) (n^a=275)	Third screening round, n (%) (n^a=265)	Aggregate, n (%) (n^a=979)
Thyroid - Differentiated and Anaplastic Carcinoma	1 (0.2)	1 (0.4)	1 (0.4)	3 (0.3)
Urinary Bladder	3 (0.7)	4 (1.5)	4 (1.5)	11 (1.1)
Vagina	0	0	1 (0.4)	1 (0.1)
Vulva	1 (0.2)	0	1 (0.4)	2 (0.2)
Cancer of Unknown Primary ^b	3 (0.7)	3 (1.1)	1 (0.4)	7 (0.7)
Other/Unknown	2 (0.5)	2 (0.7)	0	4 (0.4)
Missing	5 (1.1)	3 (1.1)	5 (1.9)	13 (1.3)

^an represents individual cancers, not participants; participants with multiple cancers may appear in multiple rows.

^bCancer of Unknown Primary is defined as an invasive cancer with ICD-O-3 behaviour code 6 or 9; or an invasive cancer with behaviour code 3, topographical code C809 and unmapped cancer label.

AJCC, American Joint Committee on Cancer; MCED, multi-cancer early detection.

Supplementary Table S12. Distribution of Stage for Cancers per First-Cancer Diagnosed.

	Positive MCED test result, cancer diagnosis, n (%)	Negative MCED test result, cancer diagnosis, n (%)	Total, n (%)
First screening round			
Total, N	419	708	1127
Stage I	88 (21.0)	345 (48.7)	433 (38.4)
Stage II	78 (18.6)	133 (18.8)	211 (18.7)
Stage III	123 (29.4)	122 (17.2)	245 (21.7)
Stage IV	103 (24.6)	56 (7.9)	159 (14.1)
Stage I-II	166 (39.6)	478 (67.5)	644 (57.1)
Stage I-III	289 (69.0)	600 (84.7)	889 (78.9)
Unstageable ^a	4 (1.0)	34 (4.8)	38 (3.4)
Missing	23 (5.5)	18 (2.5)	41 (3.6)
Second screening round			
Total, N	261	702	963
Stage 0	0	1 (0.1)	1 (0.1)
Stage I	56 (21.5)	337 (48.0)	393 (40.8)
Stage II	49 (18.8)	125 (17.8)	174 (18.1)
Stage III	75 (28.7)	140 (19.9)	215 (22.3)
Stage IV	65 (24.9)	51 (7.3)	116 (12.0)
Stage I-II	105 (40.2)	462 (65.8)	567 (58.9)
Stage I-III	180 (69.0)	602 (85.8)	782 (81.2)
Unstageable ^a	2 (0.8)	36 (5.1)	38 (3.9)
Missing	14 (5.4)	12 (1.7)	26 (2.7)
Third screening round			
Total, N	257	704	961
Stage I	58 (22.6)	330 (46.9)	388 (40.4)

	Positive MCED test result, cancer diagnosis, n (%)	Negative MCED test result, cancer diagnosis, n (%)	Total, n (%)
Stage II	37 (14.4)	143 (20.3)	180 (18.7)
Stage III	76 (29.6)	112 (15.9)	188 (19.6)
Stage IV	64 (24.9)	60 (8.5)	124 (12.9)
Stage I-II	95 (37.0)	473 (67.2)	568 (59.1)
Stage I-III	171 (66.5)	585 (83.1)	756 (78.7)
Unstageable ^a	4 (1.6)	39 (5.5)	43 (4.5)
Missing	18 (7.0)	20 (2.8)	38 (4.0)

^aUnstageable = no valid staging system exists for the combination of topo/morpho codes. Binet stages are mapped as follows: A=I, B=II, C=III; Chang stages are mapped as follows: M0=I, M1=II, M2/3=III, M4=IV.

Supplementary Table S13. Sensitivity Analysis for PPV by Screening Round and in Aggregate Accounting for Additionally Identified Recurrent Cancers.

Screening round	Number of positive tests, n	Number of participants with true-positive results accounting for only primary cancer, n	Number of participants with true-positive results accounting for additionally identified recurrent cancer, n	PPV for cancer signal detection accounting for additionally identified recurrent cancer, % (95% CI)
All test analysable participants				
First	722	419	436	60.4 (56.8, 63.9)
Second	518	261	268	51.7 (47.4, 56.0)
Third	561	257	269	48.0 (43.8, 52.1)
Aggregate	1801	937	973	54.0 (51.7, 56.3)
Participants with a prior cancer history				
First	96	35	52	54.2 (44.2, 63.8)
Second	74	32	39	52.7 (41.5, 63.7)
Third	62	14	26	41.9 (30.5, 54.3)
Aggregate	232	81	117	50.4 (44.0, 56.8)

PPV, positive predictive value.

Supplementary Table S14. Exploratory Analysis for Participants With False-positive Results with Additional Follow-up.

	Period during which cancer was diagnosed		
	Second screening round follow-up period	Third screening round follow-up period	Combined second and third round follow-up period
Number of false-positive participants in first screening round (n=303)			
Participants later diagnosed with cancer, n (%)	36 (11.9)	18 (5.9)	54 (17.8)
CSO concordance (for participants with cancer diagnosed, n=18)			
Participants with correct CSO1/2, n (%)	29 (80.6)	15 (83.3)	44 (81.5)
Participants with correct CSO1, n (%)	27 (75.0)	14 (77.8)	41 (75.9)
Number of false-positive participants in second screening round (n=257)			
Participants later diagnosed with cancer, n (%)	NA	25 (9.7)	
CSO concordance (for participants with cancer diagnosed, n=25)			
Participants with correct CSO1/2, n (%)	NA	18 (72.0)	
Participants with correct CSO1, n (%)	NA	17 (68.0)	

CSO, cancer signal origin; NA, not applicable.

Supplementary Table S15. Definitions of Screening Performance Metrics.

Term	Definition	
Participant with a false-negative result	Participant who receives a “no cancer signal detected” (negative) test result and a cancer diagnosis	
Participant with a false-positive result	Participant who receives a “cancer signal detected” (positive) test result and no cancer diagnosis	
Participant with a true-negative result	Participant who receives a “no cancer signal detected” (negative) test result and no cancer diagnosis	
Participant with a true-positive result	Participant who receives a “cancer signal detected” (positive) test result and cancer diagnosis	
Metric	Calculations	
	Numerator	Denominator
Cancer detection rate	Number of participants with a true-positive result within a given screening round	Total number of participants with an MCED test result within that screening round
Episode sensitivity	Number of participants with a true-positive result within a given screening round	Sum of participants with true-positive results and participants with false-negative results within that screening round
False positive rate	Number of participants with a false-positive result within a given screening round	Sum of participants with true-negative results and participants with false-positive results within that screening round
Negative likelihood ratio	The probability that a participant with a cancer diagnosis has a negative test result within a given screening round	The probability that a participant with no cancer diagnosis has a negative test result within that screening round
Negative predictive value (NPV)	Number of participants with true-negative results within a given screening round	Sum of participants with true-negative results and participants with false-negative results within that screening round
Positive likelihood ratio	The probability that a participant with cancer	The probability that a participant with no cancer

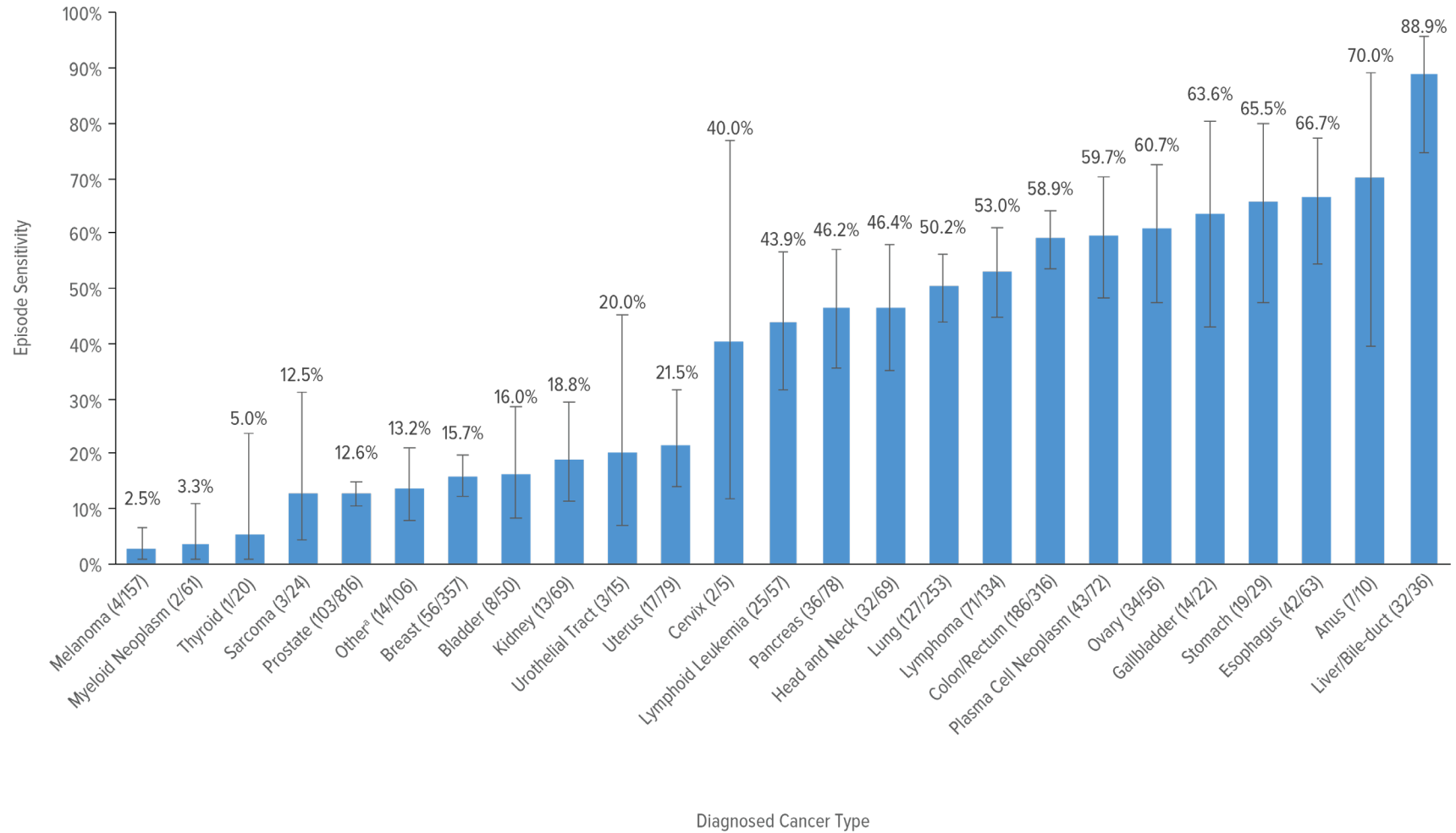
	diagnosis has a positive test result within a given screening round	diagnosis has a positive test result within that screening round
Positive predictive value (PPV)	Number of participants with true-positive results within a given screening round	Sum of participants with true-positive results and participants with false-positive results within that screening round
Specificity	Number of participants with true-negative results within a given screening round	Sum of participants with true-negative results and participants with false-positive results within that screening round

Other metrics have been defined elsewhere. Please refer to Nabavizadeh et al.¹

1. Nabavizadeh, N. *et al.* Performance and Safety of a Multi-Cancer Early Detection Test: the PATHFINDER 2 Study. *Nat. Med.* (2026).

Figures

Supplementary Figure S1. Aggregate Episode Sensitivity by Cancer Type Diagnosed.

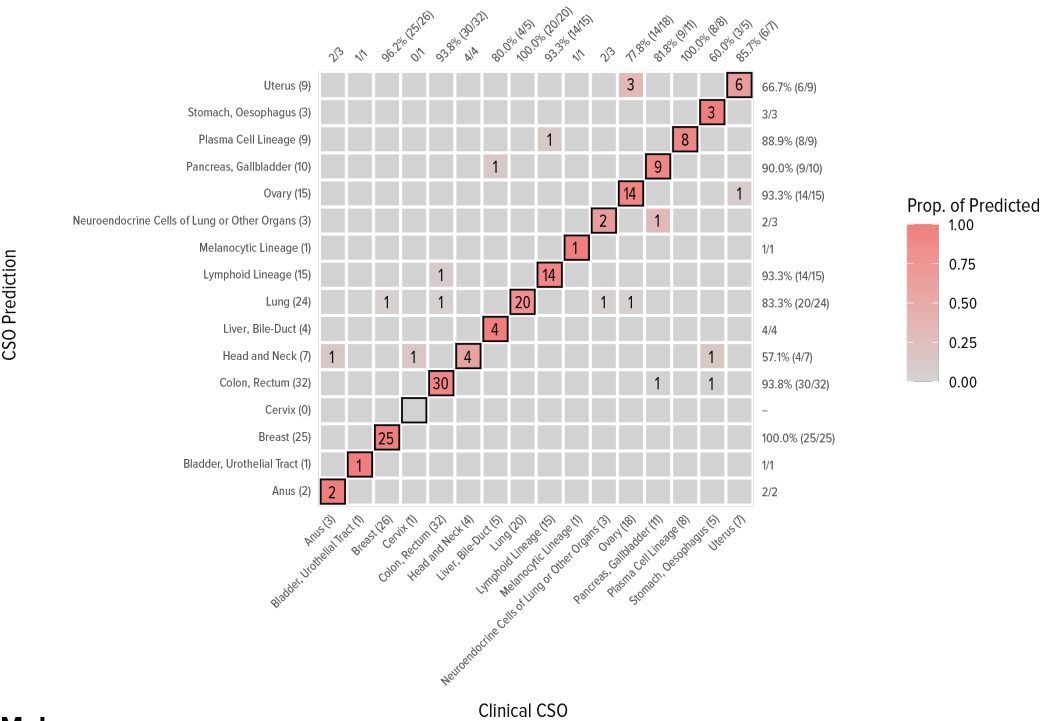


Episode sensitivity data are presented as observed percentages, calculated as defined in **Supplementary Table S15**; error bars denote two-sided 95% CIs. Cancer types with less than 5 cases are not shown.

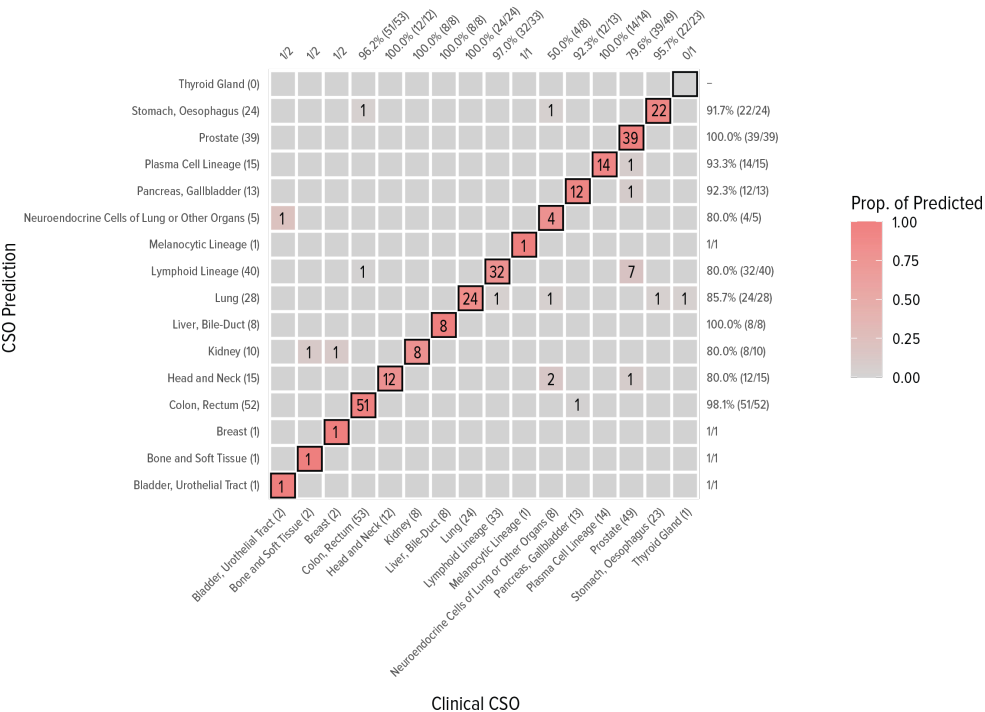
^aOther cancer types include brain (n=32), mesothelioma (n=24), small intestine (n=16), vulva (n=10), penis (n=4), skin cancer (n=4), ampulla of Vater (n=3), germ cell (n=3), thymus (n=3), adrenal (n=2), vagina (n=2), carotid body (n=1), eyelid (n=1), trachea (n=1).

Supplementary Figure S2. Confusion Matrix of Predicted CSO vs Clinical CSO by Sex by Round and in Aggregate.

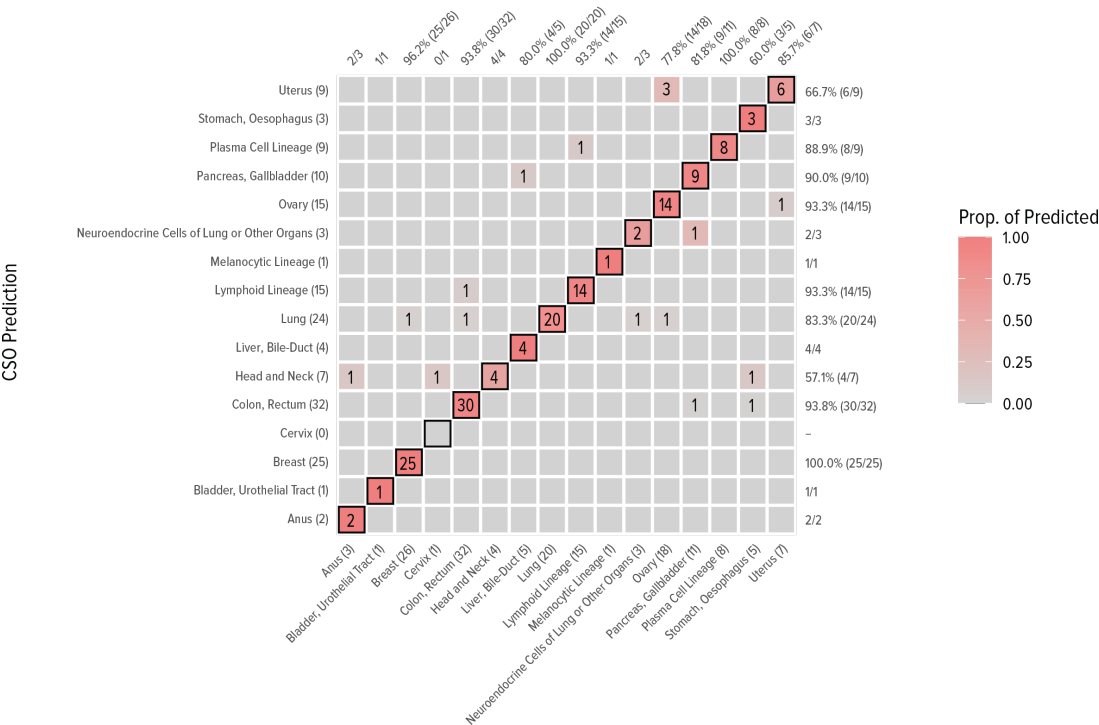
First Screening Round
Female



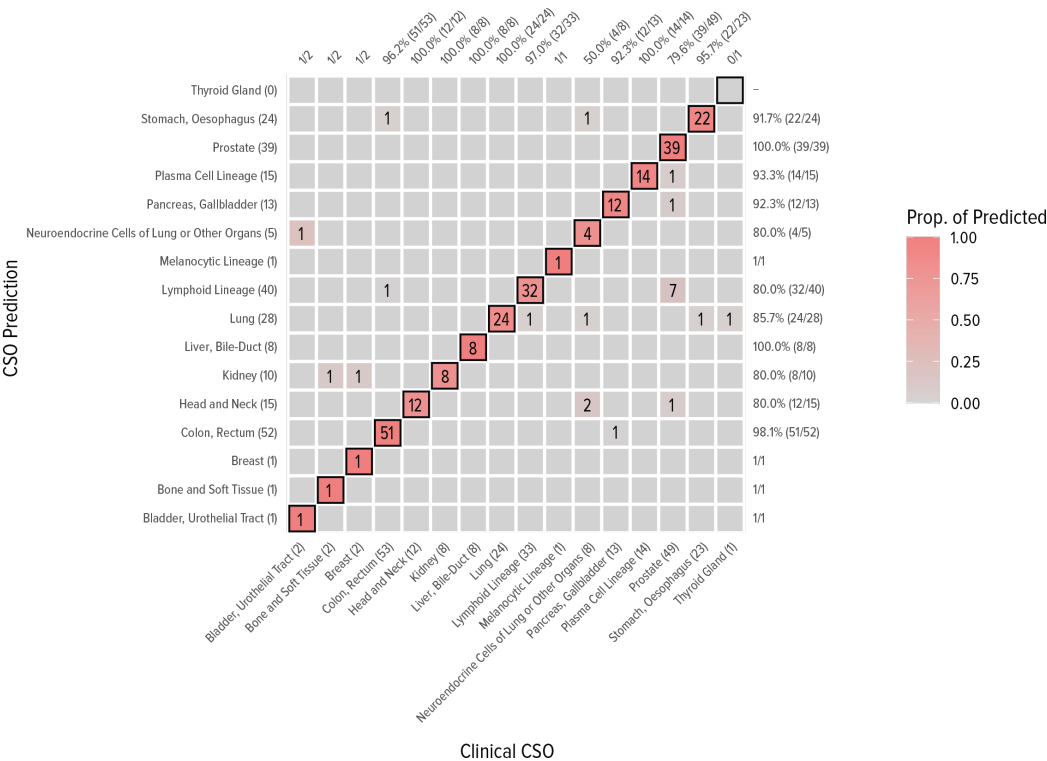
Male



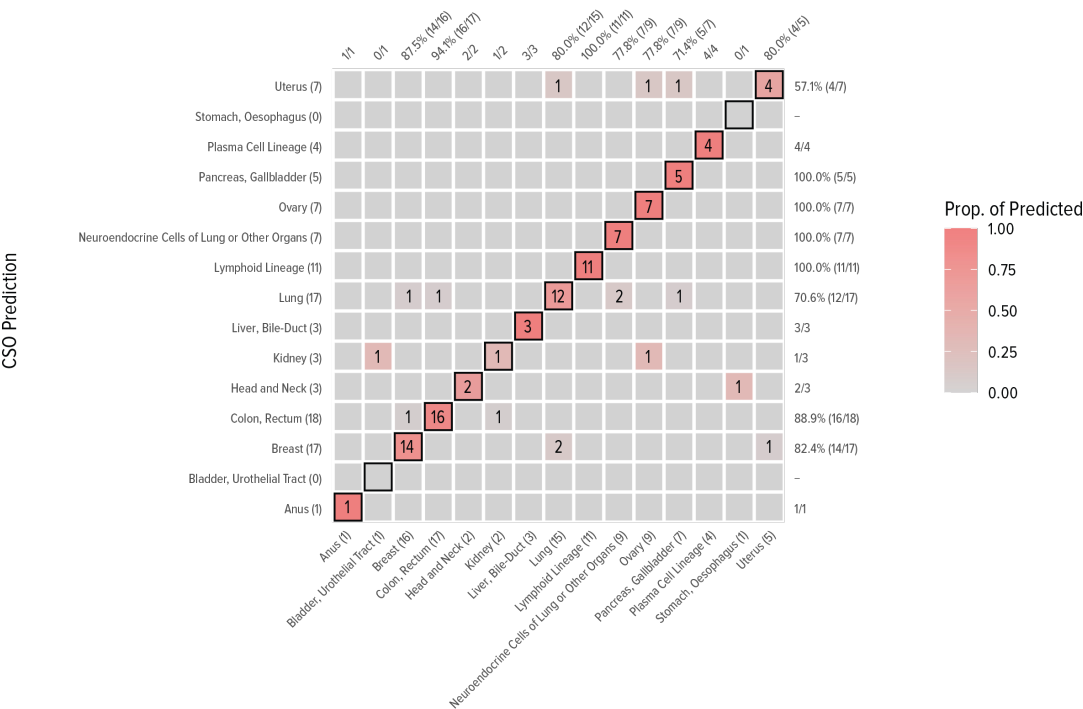
Second Screening Round
Female



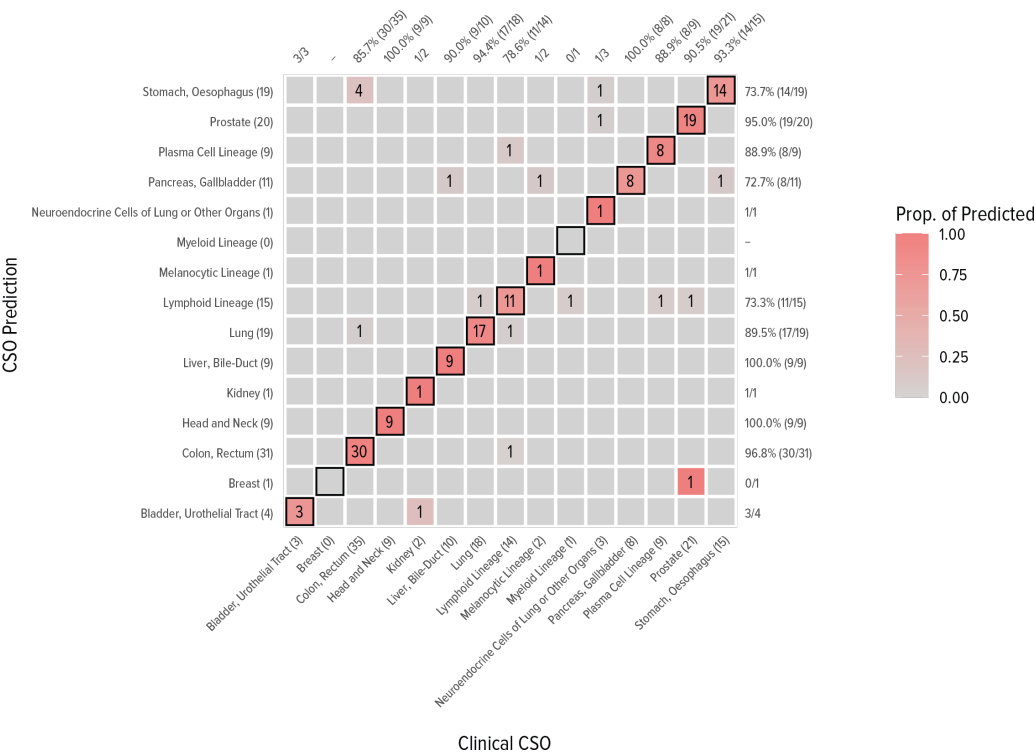
Male



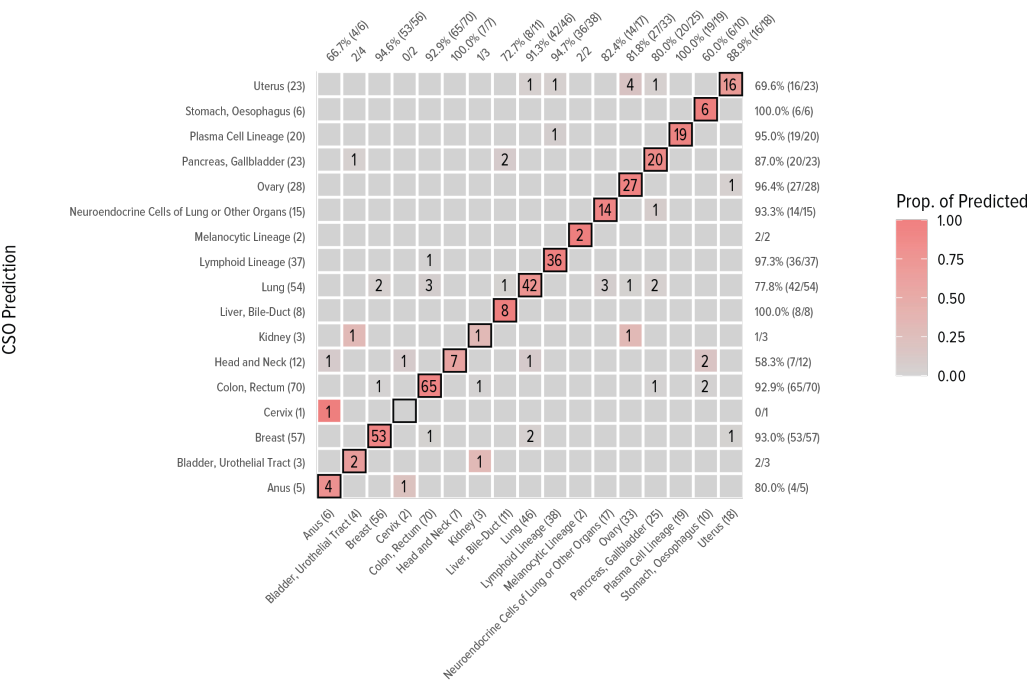
Third Screening Round
Female



Male

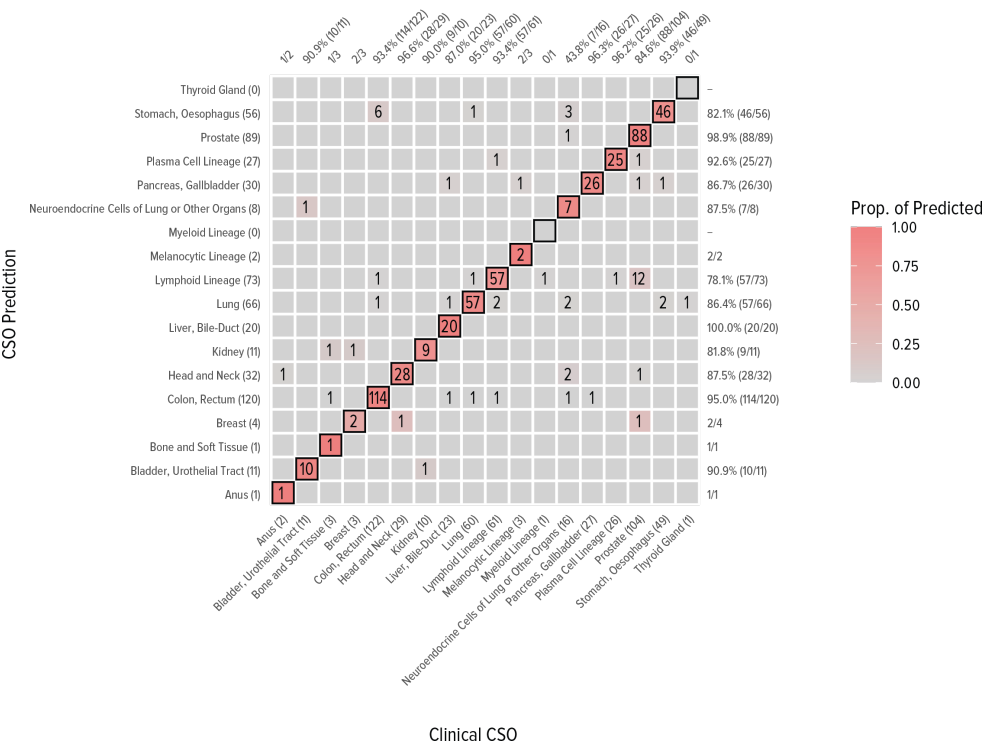


Aggregate
Female



Male

Clinical CSO

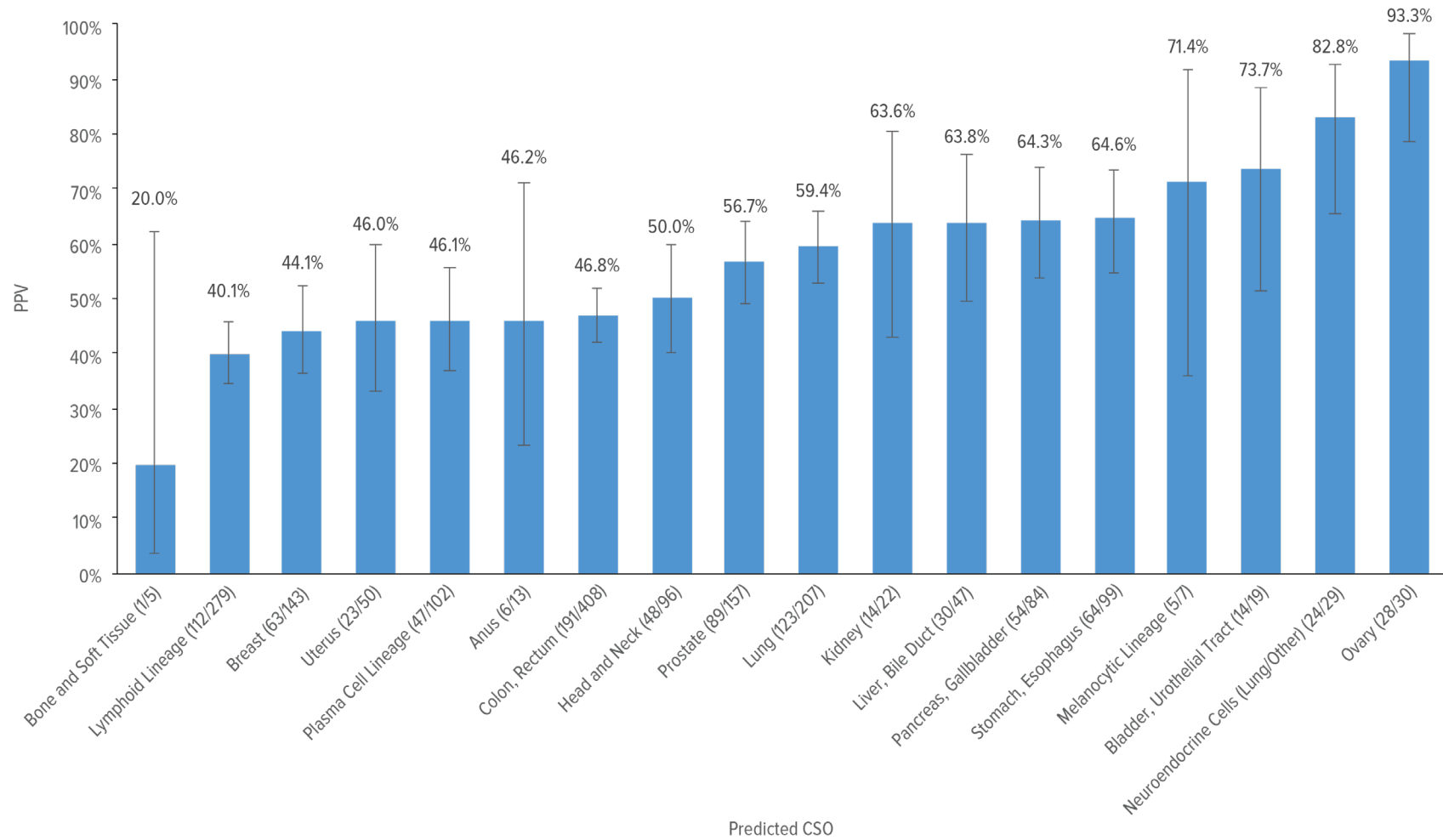


Clinical CSO

Each confusion matrix plots the number of participants for each combination of CSO prediction (y-axis) and clinical CSO (x-axis) for that round or in aggregate. Diagonal cells indicate correct CSO1 assignments (accuracy), and off-diagonal cells indicate misclassifications (errors). CSO1 prediction accuracy by clinical CSO (estimated by the proportion of the diagonal cell in each column) is indicated at the top of the matrix, and precision of each CSO prediction (estimated by the proportion of the diagonal cell in each row) along the right side. The colour is associated with the proportions of matched predicted and clinical CSOs. Metrics are not estimated for subgroups with less than 5 cases. Only CSOs with at least one prediction or diagnosed cancer are included in each matrix.

CSO, cancer signal origin; Prop, proportion.

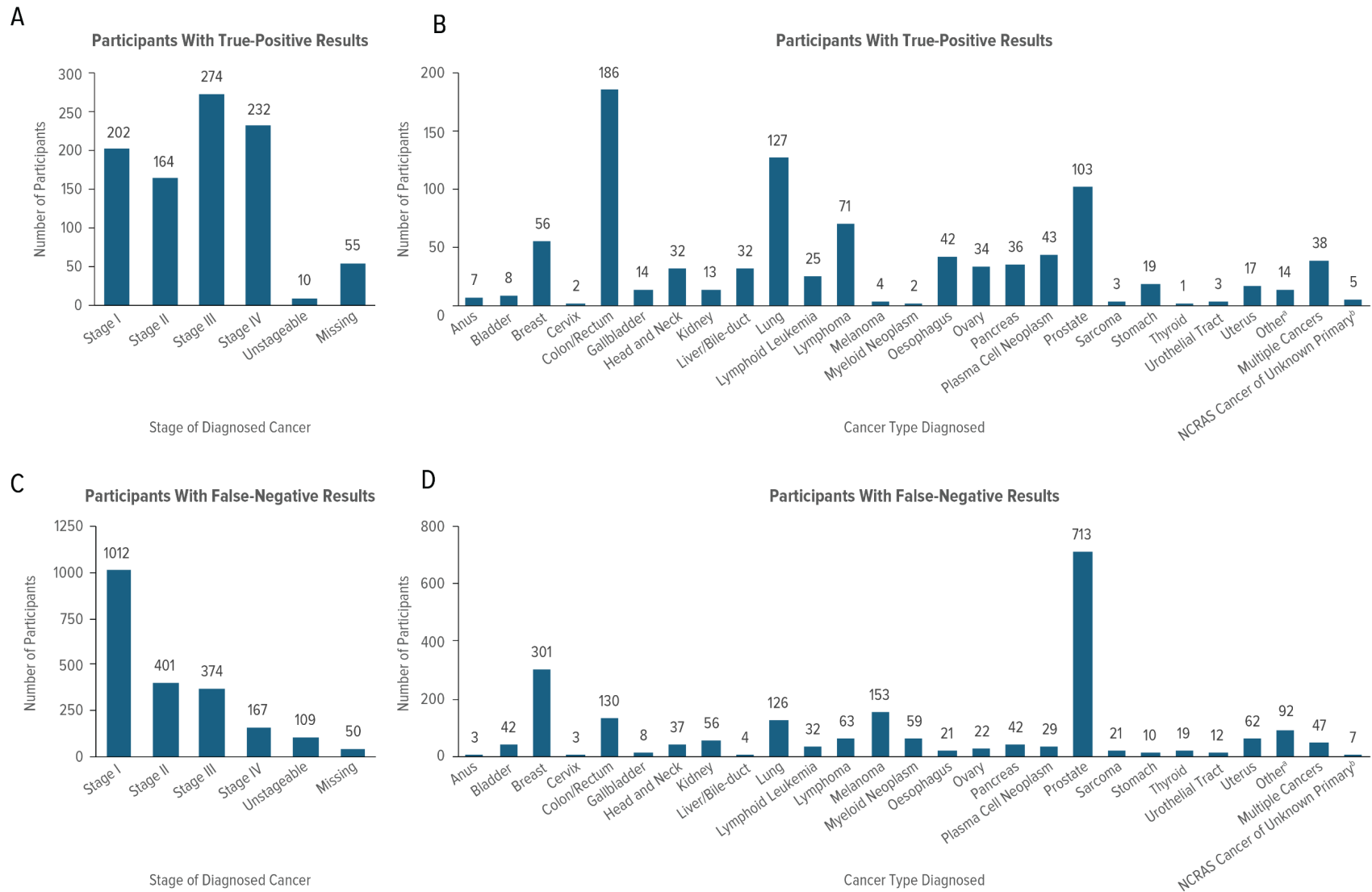
Supplementary Figure S3. Aggregate PPV by Predicted CSO.



PPV data are presented as observed percentages, calculated as defined in **Supplementary Table S15**, for each predicted CSO; error bars denote two-sided 95% CIs. Predicted CSOs with less than 5 cases are not shown.

CSO, cancer signal origin; PPV, positive predictive value.

Supplementary Figure S4. Stage and Type of Cancer Diagnosed Among Participants With True-Positive and False-Negative MCED Test Results.



- A. Number of participants across all three rounds of screening with a given stage of cancer at diagnosis who received a positive MCED test result for that round.
- B. Number of participants across all three rounds of screening diagnosed with a given type of cancer who received a positive MCED test result for that round.
- C. Number of participants across all three rounds of screening with a given stage of cancer at diagnosis who received a negative MCED test result for that round.
- D. Number of participants across all three rounds of screening diagnosed with a given type of cancer who received a negative MCED test result for that round.

^aOther cancer types include brain (n=32), mesothelioma (n=24), small intestine (n=16), vulva (n=10), penis (n=4), skin cancer (n=4), ampulla of Vater (n=3), germ cell (n=3), thymus (n=3), adrenal (n=2), vagina (n=2), carotid body (n=1), eyelid (n=1), trachea (n=1).

^bNCRAS Cancer of Unknown Primary is defined as an invasive cancer with ICD-O-3 behaviour code 6 or 9; or an invasive cancer with behaviour code 3, topographical code C809 and unmapped cancer label.

ICD-O-3; International Classification of Diseases for Oncology, 3rd Edition; MCED, multi-cancer early detection; NCRAS, National Cancer Registration and Analysis Service.